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Water Fluoridation

This information has been collated by G Mark Atkin BSc, LLB(Hons) for presentation to the Hamilton City Council on behalf of:
The New Zealand Fluoridation Information Service.
Fluoridegate Legal Action NZ

This submission is split into two parts. The first section is about section 23 of the Health Act, which is relevant to all information submitted to the Council. This is presented under Fluoridegate Legal action. The second part presents the science about fluoridation. This is presented under NZFIS.

I Part 1 – Fluoridegate Legal Action

A Standard of Proof Requirements

We make the following recommendations:

- **Ensure** that as you listen to submissions you keep in mind the question "would a reasonable person say that all of the evidence I am hearing on health risks should be ignored, or say that it is sufficient to establish a real possibility, even though the possibility may be uncertain, that there is a possible health risk from fluoride and/or the contaminant heavy metals?"

- **Note** that there is currently no confirmed legal basis for adding silicofluorides to the public water supply, as the 1964 Privy Council ruling no longer applies;

- **Note** that on the strength of current scientific evidence, adding fluoride to the water supply is likely to cause adverse health effects in significant proportions of the population, possibly all the population. As such section 23 of the Health Act requires that you cease fluoridation;

- **Note** that fluoridation arguably constitutes a nuisance. It is illegal for a council to create a nuisance. Nuisance is a criminal offence as well as carrying civil liability;

- **Note** that the addition of any amount of lead or mercury (MCLG zero); or arsenic (known carcinogen – no threshold for increased risk) is arguably "contamination" of water as defined in the LGA 2002, and creation of a nuisance, regardless of the fact that the levels remain below the allowable level, which only recognizes the impracticality of removing these compounds. Such a position is not inconsistent with the Privy Council’s ruling of 1964;

- **Note** that the Council has a statutory duty to protect residents from external health threats (such as fluoride in the water supply). Conversely, the Council does not have a statutory duty to "protect" residents from their own personal health choices (or their parents’ choices in the case of minors);
• **Note** that continuing fluoridation would place the Council at a real risk of civil and criminal liability. The Ministry of Health refuses to indemnify Councils against such liability for implementing Ministry policy;

• **Cease** your current fluoridation programme, or at least suspend fluoridation until those promoting it can convince the independent international scientific community that it is safe for all members of society, including high risk groups identified by the US National Research Council;

**Discussion**

I am aware that councils’ law firms have consistently provided unsound legal advice around fluoridation. From what I can see they have simply been lazy, repeating popular misconceptions rather than actually reading the legislation, or the Privy Council ruling of 1964. They cannot even get the year right, claiming it was ruled in 1965. If you choose to seek legal advice regarding this paper, bear in mind that you may well get advice that is equally unsound. At the time of writing this, I am aware of only one other lawyer in the country who is up with this issue. That lawyer is representing New Health NZ in judicial review against the South Taranaki District Council for its decision to fluoridate Patea and Waverley.

**Deciding Scientific Questions**

One point that comes up regularly is that councillors are concerned that they do not have the scientific expertise to decide between the scientific studies presented both for and against fluoridation. Some then take the position that they must just take the word of the DHB or Ministry of Health. This is *ultra vires*, as it abdicates councillors’ statutory authority.

In fact few if any of the presenters for fluoridation have the scientific expertise to assess the science, and equally few have actually read the original research. They simply rely on “spin” documents about the research, published by the fluoridation-promoting community.

This perception (of councillors) is exacerbated by promoters, who take two positions:

1) It is up to opponents to prove beyond any doubt that fluoridated water is seriously harmful before a council should stop fluoridation

2) If there is any harm from fluoridation, it is more than offset by the alleged benefit of reduced tooth decay.

**How section 23 of the Health Act makes your decision easier**

Fortunately for councillors it is not necessary to be an expert. This would be so if councillors had to make a decision on the basis of proof beyond reasonable doubt, or even on the balance of probabilities, as suggested by promoters.

But under section 23 of the Health Act, you are saved from this burden. Under s23 you only have to decide on **reasonable grounds** whether there is **real possibility** that fluoridation could pose a potential health risk to the community, or one or more
significant sectors of the community (such as bottle-fed infants). If so, you must stop fluoridation. There is no need to consider whether it prevents half a filling per person or not. There is no need to consider what Ministry policy is. At that point the decision is made for you.

It is important that you listen to proceedings with this in mind – would any normal reasonable person think there was a real possibility of risk? If so, your burden is discharged.

Under s23 Health Act 1956:
1) the standard of proof is not “beyond doubt”; it is “real possibility”
2) If such a health risk exists, there is no option for a council to trade off risk of harm for alleged good
3) It is irrelevant what the public think – if there is a real risk fluoridation must stop.

23 General powers and duties of local authorities in respect of public health

Subject to the provisions of this Act, it shall be the duty of every local authority to improve, promote, and protect public health within its district, and for that purpose every local authority is hereby empowered and directed—

(c) if satisfied that any nuisance, or any condition likely to be injurious to health or offensive, exists in the district, to cause all proper steps to be taken to secure the abatement of the nuisance or the removal of the condition:

It must first be determined whether fluoridation is either a “condition” or a “nuisance”. If fluoridation is likely to pose a risk to health on a reasonable person test, it is ipso facto a nuisance, so it is a rather circular argument. It is also arguable that a public water supply containing a substance likely to pose health risks is an ongoing “condition existing in the district”

So, if it is "likely" that fluoride poses health risks, the council is obliged to cease fluoridation. The standard of "likely to" has been defined by the courts as "a real, not fanciful, possibility, but not requiring a greater than 50% probability".

This embodies the precautionary approach. In relation to water supplies, this is appropriate, since the water supply reaches everyone, directly and/or indirectly.

A Ministry of Health letter from 2003, issued in response to an Official Information Request, says:

The Ministry looks for articles in publications that have been peer-reviewed and that have standing in the scientific community. That is not to say that scientists who hold opposing views to fluoride do not necessarily meet that test.”
This appears to be an issue relating to the weight of evidence on both sides...The Ministry’s assessment is that on the evidence available the known positives of fluoridation outweigh any such known adverse effects.”

This admits there are known adverse effects. These must be effects other than dental fluorosis, since the Ministry’s position is that dental fluorosis is not an adverse health effect; it is just a cosmetic effect. Under this admission, fluoridation must cease under s23, since the (allegedly) known positives cannot be considered once it is admitted there are adverse effects.

The research with which you have been presented has been published in internationally recognized peer-reviewed journals. As such it meets the Ministry of Health’s specified standard. You must therefore accept it as being as valid as the studies they quote in support of their claims. It therefore meets the reasonable person test for application to section 23.

Lastly, I refer you to the attached statement by Dr Vyvyan Howard. There is no one I know of in NZ who is qualified to contest Dr Howard’s expertise on toxicology.

2 The Precautionary Approach

This section provide background on the Precautionary Approach. Two works are attached for further reference:

1. The Precautionary Approach, Tickner and Coffin
2. The Nuffield Council Report on Medical and Bioethics

The precautionary principle is increasingly discussed in circumstances where there is some evidence that a particular activity may result in health or ecosystem damage, but great uncertainty as to the potential magnitude or nature of those impacts.

All approaches have a common theme: if there is uncertainty, yet credible scientific evidence or concern of threats to health, precautionary measures should be taken. In other words, preventive action should be taken on early warnings even though the nature and magnitude of the risk are not fully understood.

A precautionary approach to fluoridation would consider all the available evidence on efficacy, safety, and alternatives. Given the temporal (throughout a lifetime) and spatial (broad population exposure) exposure to fluoride in drinking water, a more detailed analysis of potential impacts, including population variability and identification of potentially vulnerable populations would be prudent under a precautionary framework.

(a) Discussion

This discussion is drawn from two works attached to this submission:

- Tickner and Coffin
- The Nuffield Council Report
The precautionary principle shifts the presumptions used in decision making. Rather than presume that specific substances or activities are safe until proven dangerous, the precautionary principle establishes a presumption in favor of protecting public and environmental health in the face of uncertain risks.

This places the responsibility for developing information, regular monitoring, demonstrating relative safety, analyzing alternatives, and preventing harm on those undertaking potentially harmful activities."

The Ministry of Health does not monitor any adverse health effects of fluoride across the population. It only monitors dental fluorosis, which applies to fluoride intake during the first few years of life only.

A widely cited definition of the precautionary principle is the 1998 Wingspread Statement on the Precautionary Principle.

When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

Biologist John Cairns has noted that scientists and policy makers often discount highly uncertain risks, while concluding that — unrecognized risks are still risks, uncertain risks are still risks, and denied risks are still risks.”

Dentists, as health practitioners, have a responsibility to be aware of the adverse affects of their practice on health and environment, both direct and indirect, and to prevent such affects wherever possible, while maintaining a high level of care.

Instead of asking, "What level of risk is acceptable?” or "How much contamination can a human or ecosystem assimilate before demonstrable harm?” the approach the Ministry of Health takes with fluoridation, we must ask "How much contamination can we avoid while still achieving our goals? What are the alternatives or opportunities for prevention?” and "Is this activity needed in the first place?” these are the questions we must now ask of fluoridation.

Focusing on seeking safer alternatives may also allow decision-makers to partially bypass contentious and costly debates over proof of harm.

(b) Risk identification in scientific studies

If current scientific methods result in an inability to identify early warnings of effects, or hide the great uncertainties involved in characterizing complex risks, then preventive actions can be substantially hindered.

When designing a health study, scientists make concerted efforts to avoid reaching the false conclusions that a hazardous effect exists when in fact it does not. But, an inherent consequence of minimizing this error is increasing the chances of another kind of error: missing a risk that is real.
As the late Dr Albert Schatz\(^1\) noted, scientists often focus research on the "average" individual even though there might be individuals or populations at much higher risk due to their higher exposures, genetic susceptibility, or developmental vulnerability, such as children. This was reflected in the Public Health Commission's 1995 report, and is highlighted by the American Dental Association's 2006 warning on infant formula, previously stated in the 1999 NHMRC review, and the Australia New Zealand Standard 2.9.1 for the level of fluoride in infant formula.

The limitations in scientific methods to quantify causal relationships are often misinterpreted as proof of safety. While the fine points of the scientific evidence are debated, often nothing is done about the potential hazards.

II        Part 2 – NZFIS

A       Recommendations

We recommend the Council note the following key points

1. The decline in dental decay statistics since the 1950s appears primarily due to changes in school dental practices directed by the Ministry of Health, such that significant numbers of unnecessary filling placed at that time are no longer placed.
2. At least six factors have contributed to the real decline in decay, aside from water fluoridation
3. The York Review 2000 could find little reliable evidence that fluoridation reduced tooth decay generally, that it particularly advantaged the poor, or that it was safe
4. The US National Research Council 2006 could find no level of fluoride exposure that was protective of human health
5. There is evidence that fluoridation simply delays decay by about one year, by whatever mechanism. This effect seems to disappear by about age 12 to 15. The cessation of school dental statistics collection at around age 12 means that this phenomenon, if it is real, will continue to give a false impression of permanent benefit unless more careful statistical analysis is carried out
6. No systematic review has ever found that water fluoridation benefits adults (acknowledged by Griffin 2007)
7. Fluoride does not work systemically, contrary to original beliefs
8. Fluoride is incorporated into the tooth enamel post-eruptively and topically
9. Topical incorporation occurs through application of high concentrations of fluoride, such as fluoride toothpaste, gels, and lacquers
10. Water fluoridated at up to 1ppm is too weak to provide topical incorporation
11. While the fluorapatite created through fluoride incorporation into the tooth enamel is physically harder than the normal hydroxyapatite, there is no

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\(^1\) Dr Schatz discovered the antibiotic streptomycin, the first cure for tuberculosis. The Nobel Prize in medicine was awarded for this discovery. In line with extant convention it was given to his PhD supervisor, as Dr Schatz made the discovery within his PhD research. He later developed other major antibiotics used to this day.
conclusive research showing that it is more resistant to decay. There is some evidence that it is not.

12. Latest research shows that the layer of fluorapatite is no more than 6 nm – too thin to have a permanent protective effect.

13. There is essentially no monitoring of adverse health effects from fluoridation by those responsible for it (as found by the York Review), other than dental fluorosis, which only shows fluoride exposure during early childhood.

14. The latest reviews on neurotoxicity give cause for serious concern, especially for infants, and in particular bottle-fed infants.

15. The Upper Limit of fluoride intake for infants is not based on research, but on a pro-rata basis from adult levels. As infants, especially those under 6 months of age, are more susceptible to fluoride neurotoxicity than adults, this approach is unsound.

16. The Upper Limit for adults of 10 mg per day is untenable. Adverse health effects, including Stage III skeletal fluorosis, have been shown to occur at significantly lower levels.

17. There are numerous studies showing adverse health effects from fluoride at levels of ingestion found in fluoridated communities. These are published in internationally recognized peer-reviewed journals. It is untenable to suggest they are all so fundamentally flawed that fluoridation can be declared safe.

B INTRODUCTION

Attachments:

[–The Case Against Fluoride" Connett P, Beck J, Micklem S – provided directly by Dr Connett, so not attached here]


The –York Review“ 2000

Critique of NFIS claims in its presentation to Hastings Council 2011.

1 Preamble

The scientific details of research on this issue are generally beyond the ability of the lay person to assess as to whether the research actually supports or detracts from fluoridation. One of the hallmarks of this debate is that both sides often quote the same research as supporting their case.

In this light, the best work available that addresses the science claimed both for and against fluoridation is (notwithstanding its title) The Case Against Fluoride, by Drs Paul Connett, James Beck, and Spedding Micklem. This work draws heavily though not exclusively from the NRC Review Report of 2006, and critiques the research quoted on various aspects of the debate, in a way that enables the lay person to see where the strength of evidence lies.
While this is a key strength of this work, in my view, this approach loses some of the weight and power of the research that would be appreciated by the scientific reader.

That said, it is the most helpful contribution to date to the scientific issues surrounding fluoridation.

Because fluoride is added to the water in the belief this reduces tooth decay, and has been most promoted by dental associations, the debate is seen as primarily a dental one. However, since fluoridation compounds are swallowed, the issue is in fact primarily a medical one. This continues to be overlooked by most decision makers. For example Cr Ross Jamieson, Hutt City Council, recently stated “I prefer to believe those who look in people's mouths all day.” What does a dentist see in a person's mouth that relates to neurotoxicity, premature births, heart disease, or cancer?

Given the time, resources, cost, and expertise deployed in the York and National Academy of Sciences reviews, it is beyond the means of the Council to conduct a more thorough review.

The conclusions from both these reviews were remarkably similar:
- The York Review was directed to “prove once and for all that fluoridation is safe and effective”. It looked only at population studies.
- The NRC Review was to assess “whether the 4ppm upper limit on fluoride was protective of human health”. It looked at all types of studies, including laboratory studies and medical records. While its task was to examine the 4 ppm maximum allowable level in the USA, much of the science it reviewed was relevant to fluoridation at 0.7 to 1ppm.

The York Review was only a complete study of the claimed benefits of fluoridation. It found these unproven.
It also found the safety question unproven – it could not say that fluoridation was safe. But equally, it could not say it was unsafe – because it was not allowed to look at the totality of evidence on adverse health risks.
So overall the York Review gives us a guide on the question of effectiveness, and NRC gives us a guide on health risks.

A DHB study in Onehunga 2001 showed that the more a person considered they knew about fluoridation the more likely they were to oppose it. This is contrast to a recent overseas study by Sivaneswaran and Chong. However this study looked at opinion after exposure to professional advocacy FOR fluoridation; not independent investigation. Its purpose was to identify how to persuade the public to a pro-fluoridation view. In this context “more knowledge” is actually seen as “exposure to pro-fluoridation material”. The Onehunga study is the more reliable on this point, as it canvassed lay members of the public who did their own independent private research.

The reality is that this issue will likely never be settled until the public are overwhelmingly for or against fluoridation.
FANNZ committee members have noted a significant change in public awareness on this issue since the turn of the millennium. Where the view against fluoridation was
once the “alternative” view, it has become more the “mainstream” view, outside of the health sector, which is thereby regarded with increasing distrust.

(a) Reliability of citations by the Ministry/NFIS

You need to be aware that the studies quoted by those who promote fluoridation, particularly the Ministry of Health and its new lobby group the NFIS, often do not support the claim for which they are cited as authority. They may say the exact opposite. So you need to read the actual studies before accepting them as authority. Three specific examples are:

- Cutress is quoted by Dr Robin Whyman as proving fluoridated water provides topical benefit. This study did not address topical effects – it stated it was based on the assumption of systemic benefit, now accepted as disproved.

- Crosby 1969. This is cited as showing silicofluorides dissociate completely into free fluoride ions in water. In fact Crosby found an 87% dissociation with one method, and 95% with the other. All other work cited as supporting the claim ultimately trace back to Crosby – clearly they have never read Crosby.

- Griffin 2007. This does not say that fluoridation reduces adult tooth decay by 27%, as claimed by Dr Robin Whyman. Moreover, the total claimed saving is refuted by official statistics.

I have attached a critique of a presentation deployed on the NFIS website, to highlight some of their key deceptions.

(b) Oral Health Survey 2009

This was not research. The authors did not conduct any scientifically valid research on fluoridation. Their conclusion that there is no difference in dental fluorosis rates between fluoridated and unfluoridated communities is refuted by the two recent studies completed on this, both of which found a doubling in dental fluorosis rates with fluoridation.

(c) ESR 2000

In 2000 the Ministry of Health commissioned ESR to provide a review of research since the PHC review in 1994. The terms of reference included review of any internationally published peer reviewed studies into adverse health effects of fluoridated water. The review is limited to the same issues addressed by the PHC 1994 review and omits leading research such as that of Mullinex and Masters and Coplan. It covers only 14 studies from the 6 year period, reaching a general

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3 Official Information Act response (Minister of Health, 3 April 2001), 2.
conclusion that no harmful effects have been shown from fluoridation since the 1994
PHC report. Yet it had focussed on only two areas of concern and sourced the same
databases as the PHC had noted were unlikely to adequately cover adverse
research.  

It also evidences bias and factual errors. Firstly, in reviewing hip fracture studies it
respectively accepts a pro-fluoridation study and rejects an anti-fluoridation study
after identifying in identical terms the same methodological defect. To be
scientifically objective it would have to reject both studies if its criticism was sound.
As an example of factual error, ESR state that their view that there is no relationship
between hip fracture and fluoridation is supported by the Melbourne review 1999, yet
this review specifically found that the question remained unresolved and
recommended further epidemiological study on Australia's population.

This review fails to meet its terms of reference and is potentially misleading to any
decisionmaking body.

(d) SCHER report.

This was seen as a predetermined outcome from the start. Its reports were regularly
self-contradictory. Its report claimed –There are only limited data on the neurotoxicity
of fluoride in experimental animals." Yet it had received over 100 references to such
studies. When asked to explain its misrepresentation it declined to answer.

A critique of SCHER's unscientific handling of the issue can be found at:

http://www.fluoridealert.org/scher-fan-review-2011.html

C Cost Effectiveness of Fluoridation

Attachments

Griffin – Fluoridation and Adults 2007

Komarek – delayed tooth eruption 2005

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8 Compare the 1592 the PHC identified for a comparable timeframe.
9 This is of particular concern. These are the two principal medical databases used by the medical
fraternity: if they selectively exclude fluoride-adverse research as the PHC suggest and that same
medical fraternity promotes fluoridation, how can any decisionmaker be properly and objectively
informed of all the issues?
10 Institute of Environmental Science and Research Ltd. Fluoridation of Water Supplies –an Evaluation
of the Recent Epidemiological Evidence (September, 2000) (ESR Review); compare at 14 & 16.
11 ESR Review
12 Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements
13 Zeigelbecker R —Lgnormal Distributions – a Theoretical Model for Biomonitoring”. Dental data
from WHO published in Fluoride 26 1993 p263-266
Is Fluoridation Effective at All?

For a cost-effectiveness analysis to be conducted, it must first be determined whether water fluoridation is effective at all.

The US Centers for Disease Control and Prevention has claimed that "fluoridation is one of the top 10 public health achievements of the 20th Century." This statement came from an internal memo in its oral health branch. The CDC has consistently refused to support the claim with scientific evidence. Nevertheless, fluoridation promoters repeat it like a mantra.

Fluoridation was based on the work of H Trendley Dean DDS. He claimed that areas with higher fluoride levels had less tooth decay.

In 1955 Dean admitted under oath, that his data purporting to prove the fluoridation hypothesis were not valid. (H. Trendley Dean: Proceedings, City of Oroville vs. Public Utilities Commission of the State of California, Oroville, California, Oroville, California, October 20-21, 1955.)

It was shown that Dean had selected the cities that would give a positive result for fluoride. When all available data was examined it was found there was a scatter pattern – no relationship at all (Rudolf Ziegelbecker).

Dean's chart:
The following chart is from Zeigelbecker, using all data. The vertical axis is DMFT. The "wrong conclusion" is Dean's line:

**FIG. 2: CARIES INCIDENCE OF CHILDREN IN 21 CITIES OF 4 IN USA IN RELATION TO THE NATURAL FLUORIDE CONTENT OF DRINKING WATER (DATA OF DEAN 1941/42)**

The following chart is from Zeigelbecker, using all data. The vertical axis is DMFT. The "wrong conclusion" is Dean's line:
And again, no correlation between DMFT and fluoride concentration:\(^\dagger\)

Fluoridation promoters typically say that there was even more data available and if Ziegelbecker had used that it may have shown a correlation. But that is nothing more than wishful thinking. They have never done the wider analysis, so must accept the analysis available.

\(^\dagger\) Ziegelbecker R —Lognormal Distributions – a Theoretical Model for Biomonitoring". Dental data from WHO published in *Fluoride* 26 1993 p263-266
This study found no difference in tooth decay regardless of whether the children consumed fluoridated tap water or unfluoridated bottled water. We provide the abstract verbatim:

**ABSTRACT**

(i) **OBJECTIVES:**

Bottled water consumption in the United States has greatly increased in the past decade. Because the majority of commercial bottled water is low in fluoride, there is the potential for an increase in dental caries. In these secondary data analyses, associations between bottled water use and dental caries were explored.

(ii) **METHODS:**

Subjects (n = 413) are in the Iowa Fluoride Study, which included dental examinations of the primary (approximately aged 5) and early erupting permanent (approximately aged 9) dentitions by trained dentist examiners. Permanent tooth caries and primary second molar increments were related to bottled water use using logistic and negative binomial regression models. All models were adjusted for age and the frequency of toothbrushing.

(iii) **RESULTS:**

Bottled water use in this cohort was fairly limited (approximately 10 percent). While bottled water users had significantly lower fluoride intakes, especially fluoride from water, there were no significant differences found in either permanent tooth caries (P = 0.20 and 0.91 for prevalence and D(2+FS, respectively) or primary second molar caries (P = 0.94 and 0.74 for incidence and d(2+fs increment, respectively). Results for smooth surfaces differed somewhat from those for pit and fissure surfaces, but neither showed significant differences related to bottled water use.

(iv) **CONCLUSION:**

While bottled water users had significantly lower fluoride intakes, this study found no conclusive evidence of an association with increased caries. Further study is warranted, preferably using studies designed specifically to address this research question.

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2 Effectiveness or otherwise of fluoridation.

(a) Mode of action
When fluoridation was implemented it was believed that it worked by being taken into the bloodstream and incorporated into tooth enamel during formation. There was never any scientific basis for this – it was just an assumption, treating fluoride as if it were an essential nutrient like iron.

This belief was disproved in 1999. It is now internationally accepted that any benefit from fluoride is by surface application; not by swallowing:

Featherstone published his research in 1999\textsuperscript{13} and later in the Journal of The American Dental Association. Featherstone states:

- Fluoride works primarily via topical [surface-acting] mechanisms... The level of fluoride incorporated into dental mineral by systemic ingestion [drinking] is insufficient to play a significant role in caries prevention”.

- Until recently the major carries-inhibitory effect of fluoride was thought to be due to its incorporation in tooth enamel during the development of the tooth prior to eruption. This supposed mechanism was behind public health efforts (such as water fluoridation). There is now overwhelming evidence that the primary carries-preventive mechanisms of action of fluoride are post-eruptive through ‘topical’ effects for both children and adults”. (emphasis added)

- The topical effects of fluoride are over-riding, and the systemic incorporation of fluoride in tooth mineral is unfortunately not a major benefit”.

- The concentration of fluoride in dental enamel and dentin provided by fluoridation of drinking water or by natural fluoride levels at about 1ppm is insufficient to provide protection against caries.” The effects are all via the [topical] mechanisms of inhibition of demineralization, enhancement of remineralization and action on bacteria.” (emphases added)

Featherstone describes that the benefit from fluoride is from continued elevated levels in the saliva and plaque caused by initial application of high concentration fluoride such as in toothpaste.

Other researchers stated "By 1981, it was therefore possible to propose a paradigm shift concerning the cariostatic mechanisms of fluorides in which it was argued that the predominant, if not the entire, explanation for how fluoride controls caries lesion development lies in its topical effect on de- and remineralization processes taking place at the interface between the tooth surface and the oral fluids. This concept has gained wide acceptance... With today's knowledge about the mechanisms of fluoride action, it is important to appreciate that, as fluoride exerts its predominant effect... at the tooth/oral

\textsuperscript{13} Featherstone J.D. —Prevention and reversal of dental caries: role of low level fluoride”
fluid interface, it is possible for maximum caries protection to be obtained without the ingestion of fluorides to any significant extent."\textsuperscript{14}

The CDC acknowledges that fluoridated water has no cariostatic effect:

—The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low --- approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas (27). This concentration of fluoride is not likely to affect cariogenic activity.”

The CDC and other fluoridation promoters continue to claim that small amounts of fluoridated water being swallowed throughout the day provides dental protection. However there is no scientific basis for this that has come to light since 1999. This claim appears to simply be the only way of hanging onto fluoridation policy.

The following studies show that fluoridated water is to low in fluoride to provide any topical benefit:


Cutress, T.W. (1995) "Effects of fluoride-supplemented sucrose on experimental dental caries." \textit{Advances in Dental Research} 9(1). (Note – Cuttress is a NZer)


(b) Claims of topical benefit by NFIS

Dr Whyman provided the following references as supporting topical benefit from fluoridated water:


We have obtained copies of only two of these studies.

Number 7 (Cutress et al). Not only does this study NOT ADDRESS the means by which fluoride gets into tooth enamel, it quite clearly states its assumption that it is by systemic incorporation. In no way does it support Dr. Whyman’s claim. Either Dr. Whyman has never read this study, or he is deliberately bluffing.

Number 2 (Ten Cate and Featherstone). This study found topical benefit to dead tooth enamel in vitro, but acknowledged that tooth enamel in the mouth behaves differently, and therefore the results could not be claimed applicable to live teeth subjected to fluoridated water.

Regarding the studies, we note that studies one and two were by Featherstone, before his 1999 publication, which refutes topical benefit from fluoridated water.

We understand number 3 is a variation of his 1999 publication, so it is highly unlikely that he states a reversed his position in that timeframe.

Numbers 4 to 6 predate Featherstone’s 1999 publication, which refutes them.

We are unable to comment on number 8.

However, given there are 5 studies clearly showing that fluoridated water has no topical benefit, and that the two references we have been able to check do not support topical benefit from fluoridation, the balance of science today must be taken that it does not, unless promoters can provide the other studies for the Council’s examination. To date they have refused to supply them, on the grounds of copyright.

(c) Is fluorapatite more resistant to decay?
There is an ongoing question whether fluorapatite, although physically harder than hydroxylapatite, is more resistant to decay.

Dr. John Yiamouyiannis writes in *Fluoride the Aging Factor: How to Recognize and Avoid the Devastating Effects of Fluoride:*

"Brekhus from the University of Minnesota Department of Biochemistry published a study in which they claimed that the enamel of sound teeth had a significantly greater fluoride content than the enamel of teeth with cavities. But 25 years later, Dr. Armstrong was forced to admit that these results were false. In a follow-up study in 1963, Dr. Armstrong found no difference in the fluoride contents of the enamel of sound and decayed teeth."

The Centers for Disease Control and Prevention states "The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries." 15

Leaving that aside, recent research shows that any surface layer of fluorapatite is likely no more than 6 nm thick. This can wear off in a single chewing, and it is dubious whether it provides protection.16

The fluoridation affects the surface only on the nanometer scale, which is in contrast to recent literature with respect to XPS analysis on dental fluoridation, where depth profiles of F extending to several micrometers were reported. In addition to the elemental depth profiles, as published in various other studies, we also present quantitative depth profiles of the compounds CaF(2), Ca(OH)(2), and fluorapatite (FAp) that were recently proposed by a three-layer model concerning the fluoridation of HA in an acidic agent. The analysis of our experimental data exactly reproduces the structural order of this model, however, on a scale that differs by nearly 2 orders of magnitude from previous predictions. The results also reveal that the amount of Ca(OH)(2) and FAp is small compared to that of CaF(2). Therefore, it has to be asked whether such narrow Ca(OH)(2) and FAp layers really can act as protective layers for the enamel."

It appears this may have been known as far back as 1979:

—One of the disadvantages is that the [conventional methods of applying fluorine compounds to the tooth surface] are not always completely effective. In order to change hydroxyapatite into fluorapatite which is


resistant to acids, a perfect reaction must be effected by bringing the fluorine ion (F-) sufficiently into contact with the crystal structures. But mere application of the fluorine compound to the enamel results in only a slight degree of formation of fluorapatite on the surface layer of the enamel with a strong possibility that the hydroxyapatite will not be fully fortified with a decay resistant property. Particularly, little or no fluorine ion (F-) goes into the enamel and no fluorapatite is produced at all. Accordingly, the remaining texture on the tooth surface is corroded by acids, melts and falls off to thereby bring a new hydroxyapatite texture into direct contact with acids, thus furthering the state of tooth decay, contrary to the original intention. “17

(d) Background Factors and Policy changes affecting dental practices and recorded dental statistics

(i) Summary
The majority of the reduction in tooth decay statistics is due to cessation of the unnecessary filling of teeth by school dental nurses – a practice that appears to have arisen with the formation of the Service. This led to an artificial increase in decay statistics leading up to the Hastings experiment

Based on the NZ figures, the actual reduction in tooth decay since fluoridation began appears to be on the order of 2.3 DMFT, compared with a recorded decline in decay statistics of around 12 DMFT.

There are six factors other than water fluoridation that it is commonly agreed have contributed to this reduction, discussed in this section.

If fluoridation contributed at all, it is likely to be minimal, and that does not allow for either the higher average socioeconomic status of fluoridated children, or merely delayed decay.

This contrasts starkly with the perception, perpetuated by the Ministry of Health and the NZ Dental Association, that the reduction of around 15 DMFT is due to water fluoridation. It explains why people have the false belief that because they had a lot of (unknown to them, unnecessary) fillings and their children and grandchildren have few, that this must have been due to fluoridation. In fact, most of the reduction is due to a reversal of inappropriate dental practices.

(ii) Declining tooth decay statistics – Background Factors

Since the 1930s tooth decay statistics have declined across the developed world, at similar rates, and to very similar final levels today. This has occurred in countries that:

1. Have normal levels of fluoride in their water (less than 0.3 ppm)
2. Artificial fluoridation at around 1ppm since the 1940s and 50s
3. Natural fluoride levels at around 1ppm

In the third group fluoride cannot, logically, have had any part to play as these levels have presumably remained unchanged for hundreds or thousands of years. Any imported beverages made with fluoridated water will be at the same fluoride level at that naturally occurring, so these will not change total fluoride exposure.

This reduction has two components:

1. Changes in dental practices that have reduced the number of unnecessary fillings placed without any change in actual tooth decay rates
2. Changes in a range of factors that have reduced the actual incidence of decay.

WHO Figures 1965 to 2004

Reduced Tooth Decay With or Without Fluoridation - WHO Figures
(iii) Changes in factors affecting decay

There are a number of factors believed to have reduced tooth decay:

1. The advent of refrigeration, reducing the bacterial count in food
2. Increased consumption of cheese, which appears to have a protective effect on teeth (aside from its calcium content)
3. Increased socioeconomic levels across the developed world
4. Use of antibiotics
5. Better oral hygiene knowledge and practices
6. Use of fluoride toothpaste
7. Fluoridation of water

The first five are generally accepted. Use of fluoride toothpaste has been generally accepted, but is now under some question. Water fluoridation is has been contested since its inception.

Dr Robin Whyman, representing the Government Health agencies, advises that he accepts the first six factors have contributed to improved oral health. He believes that water fluoridation has provided a benefit over and above the background reduction in decay resulting from the other factors.

As the York Review found, there is no conclusive evidence for this belief.

(iv) Changes in dental practices

In 1921 NZ began training dental nurses, to form the school dental service. It was so successful that other countries, such as the USA followed the model.

It seems the dental nurses were overzealous in filling teeth.
First, they filled tiny surface defects in the enamel, which are always present and usually remineralise naturally.

Second, the drilled and filled perfectly healthy teeth – generally the grinding surface of molars. This was called "preventive filling": drilling and filling perfect teeth to prevent them getting decay, which would result in a probably smaller drilling and filling.

The result was a dramatic increase in DMFT scores without any corresponding increase in actual decay. In other words the measure of decay (DMFT) no longer measured actual decay, but basically the number of fillings, many of which were completely unnecessary.

This is shown in the following statistics from H T Dean's famous 21 cities. It is also how "tooth decay" reduced so dramatically after fluoridation began – by not placing these unnecessary fillings, which in turn was falsely attributed to fluoridation. Note the comparison 6 – a 3-fold increase in "tooth decay" between 1933 and 1945. In NZ, according to a 1968 New Zealand Health Department Survey of young people, those 15 years old averaged 13
amalgam fillings and those 21 years old averaged 16 fillings at that time\textsuperscript{18}.  

\textbf{Fig. 18}

\textbf{Change of dental caries prevalence data in the 6 cities with low and 1 city with high fluoride concentration in drinking water between 1933/34 and 1941/42. All cities are from the ”21-cities-study” by H.T. Dean et al 1941/42.}

During the Hastings experiment in the 1950s, the NZ health Department instructed dental nurses to stop filling tiny surface defects in teeth. This led to an overnight 25\% reduction in DMFT scores. This was falsely attributed to fluoridation, after it became apparent that there was no real benefit from fluoridation in the experiment. The change was never revealed to the public. It was uncovered under the Official Information Act by Dr John Colquhoun in 1984. The following letter was written just 2 years before the experiment ended.

\begin{center}
\textit{D.R. Beck, Dental Health: Status of the NZ population in late adolescence and young adulthood, Department of Health. Special Report Series 29 (1968).}
\end{center}
It is clear from this that the experimenters were determined to show fluoridation was beneficial before the experiment began – a commitment of some kind to the USA apparently. To achieve this, they received advice from F A Arnold Jr, who had fudged the Grand Rapids experiment in a way that was adopted for Hastings – remove the control city (Muskegon in the US and Napier in NZ) that was showing a similar decline in tooth decay to the experimental city, and report the decline only on a "before and after" basis, claiming the reduction was due to fluoridation.

Then, in 1976, the NZ Health Department issued an instruction to drill only teeth showing signs of decay. This resulted in a 30% reduction within 1 year (i.e. by 1977) and a nationwide 64% reduction in amalgam fillings placed over the next 5 years i.e. to less than 8 fillings by 1981.\(^\text{19}\)

This explains why there was no perceptible benefit from fluoridation in NZ from 1985 to the mid 1990s, when Betty de Liefde published her research in the NZ Dental Journal (1998)\(^\text{20}\) – the artificial "reduction" allowing "before and after" studies to report a decline in decay had ceased, and where dental nurses in unfluoridated areas would have been more likely to take a "precautionary" approach to filling healthy teeth.

\(^{19}\) B. De Liefde, The decline of caries in New Zealand over the past 40 years, New Zealand Dental Journal 94 (1998), 109-113 (De Liefde)

\(^{20}\) De Liefde,
The following chart has been prepared to give a fair representative indication of the real decline in tooth decay since 1954, as compared to the decline in dental statistics. It is not exact as we only have reported figures at fixed dates. As can be seen, the likely decline in actual decay is small compared with the decline in decay statistics.

![tooth decay vs reduced decay statistics](image)

3  **Delayed Decay and Delayed Tooth Eruption**

(a)  **The Theory**

Teeth only become susceptible to decay once they have erupted into the mouth. Consequently, a delay in eruption will have two effects on data when comparing children with the delay with children of the same chronological age without the delay:

1. They will have less teeth, and therefore less total decay even if they have the same percentage decay per tooth;
2. The erupted teeth will have had one year less exposure to decay causes, hence less decay per tooth.

DMFT data is only ever collected and reported as a total, based on children of the same chronological age. This therefore gives lower decay figures even though there has been no benefit.

Also, oral health statistics are collected through the school dental service, at ages 5-6 and 12-13. There is considerable evidence that fluoridation simply delays tooth decay by about 1 year. Since delayed decay effects disappear somewhere between the ages of 12 and 15, this will never be picked up by those statistics, leading to the false belief that fluoridation is actually reducing decay. It seems most likely that this is in turn caused by a delay in tooth eruption caused by fluoride. This is not conclusively proven, however the key point is that, whatever the cause, the temporary delay appears to occur. This is consistent with studies such as Armfield and Spencer 2004, Newbrun 1989, Brunelle and Carlos 1990.
There have been many studies indicating a delay in eruption due to fluoride. It is speculated that, as fluoride is an enzyme inhibitor, it inhibits the enzyme that dissolves the roots of the deciduous teeth, delaying their falling out, which in turn delays the adult teeth from erupting to replace them. The first confirmation was Feltman and Kosel in 1961, following a 14 year study.

If delayed eruption is a reality, the whole belief in fluoridation has been based on an illusion, albeit initially an understandable one. All studies that have not allowed for this effect must be scrapped, and all claims of benefit from fluoridation based on these studies abandoned as unscientific. This leaves only one study – the Komarek study of 2005, which showed no benefit when allowing for this delay. This is discussed below.

(b) The Science

All claimed benefits from fluoridation can be accounted for if, as the evidence now shows on the balance of probabilities to be correct, fluoridation simply delays eruption of the teeth through the gums by about 1 year. Promoters have had 60 years of data to disprove this effect, but have not done so. They have just repeatedly denied it. In fact, as we will see, they have actually data confirming it.

According to the York Review (McDonagh et al. 2000):

- No study used an analysis that would control for the number of erupted teeth per child” (p.24)

The 1999 Review for the Australian National Health and Medical Research Council Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements states:

- Some evidence exists that tooth eruption is delayed in fluoridated areas. It has been suggested that a proper comparison of caries rates should involve children one year older in fluoridated areas than in non-fluoridated areas.”

The following chart shows the actual records of this UK study, with the non-fluoridated data also shown moved by just over one year. If there had been a genuine benefit, the lines would have continued to diverge. The fact that they are parallel shows only a delay in decay; not a reduction.
The Brunelle and Carlos study was the largest study ever conducted in the USA, on about 40,000 children. Again, if the results are shifted to allow for a year's delay in eruption, the lines are essentially identical, as in the UK study, showing no real benefit. The original analysis based on the age of the child (left) appears to show benefit, which disappears when the unfluoridated data is shifted by one year to allow for delayed eruption.
While many studies, including animal studies, have indicated a delaying effect, the definitive study is that of Komarek, published in 2005.

Komarek’s study:
1. Confirmed there is an approximately one year delay in tooth eruption due to fluoridation, and that this varies between individuals, possibly on a genetic basis

2. Once the delay in eruption is adjusted for, there is no difference in tooth decay rates.

Komarek used the severity of dental fluorosis as the basis for classifying fluoride exposure, as questionnaires on fluoride exposure, normally used, are unreliable. Further, if there were individual differences in susceptibility to fluoride, these would have been automatically corrected for by this method.

Komarek showed a 1 year delay, and that once the erupted age of the tooth was used for comparison, there was no difference between fluoridated and unfluoridated children.

Most tooth decay occurs within the first three years after tooth eruption. So the effects of a 1 year delay will disappear after 4 or 5 years. The permanent teeth begin erupting from around age 5, and most have erupted by age 12.

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Consequently, the temporary apparent benefit will still be in evidence. It would not be detected unless dental statistics were collected again at 16-18. Armfield and Spencer\(^22\) found no difference in the permanent teeth from age 12. Masters and Coplan found the same at age 15. This is precisely the age range where the delayed effect would be significantly subsiding. The ESR report 1999 similarly showed a temporary small extra benefit to the poor, subsiding significantly by age 13. By extrapolation this would have been zero by age 14.

(e) The early American studies

From the day the United States Public Health Service (USPHS) completed their original 10-year Newburgh and Kingston (New York) fluoridation experiment, fluoride promoters have repeatedly claimed that fluoride added to drinking water can reduce tooth decay by as much as 60 to 70%. They arrived at that figure by misreading the statistics. This is how they did it:

They ignored the fact that fluoride interferes with proper growth of children’s permanent teeth, which causes the teeth to erupt later than normal. Teeth that have not yet erupted cannot decay, therefore, at first (at age 6) the fluoridated Newburgh children had 100% less tooth decay, by age 7 also 100% less, age 8 - 67% less, age 9 - 50% less, and by age 10 - 40% less. Realizing their experiment was going downhill, the USPHS stopped their experiment early, totaled the five reductions shown, then divided by 5 to obtain what they called "an over-all reduction of 70%." Obviously, the only reduction that really counted at that time was the 40% (age 10).

Had the Health Department continued their survey beyond age 10, they would have found that the percentage of reduction continued down hill to 30%, 20%, 0%, and eventually these children had more cavities — not less. The rate of decay is identical, once the children’s teeth erupt. (See 4-1: "Fluoridation Benefits — Statistical Illusion." Testimony of Konstantin K. Paluev, Research and Development Engineer, Mar. 6, 1957).

John A. Forst, M.D., a New York public health official, found that after ten years of fluoridation in Newburgh, 63.2% of the school children had decayed teeth compared with fluorine-free Kingston, which had only 41.7% with tooth defects. (See 4-2: statement from John A. Forst, M.D., from The University of the State of New York, Oct. 26, 1954).

Data by Dr. David B. Ast, who was in charge of the fluoridation experiment (Tables, page 319, *Journal American Dental Association*, 1961) shows delay in decay only until age 15. Then Newburgh passes non-fluoridated Kingston in decayed and filled teeth, after 16 years of fluoridation. Newburgh, with a 9%
increase in population, added 18% more dentists. Kingston, with 1% increase, dropped 3% of its dentists. (See 4-3: statement and chart).

This "65% less dental decay" is just a statistical illusion. When the Health Department’s own statistics are read correctly, they prove that fluoridation merely causes a temporary delay in decay. (See 4-4: Fluoridation Fallacies — Exposé of Fluoridation Claims Based on Advocates Own Statistics, by Charles Klint). By ignoring this delay factor, the fluoride promoters have continued reading statistics incorrectly to this day.

(f) Armfield and Spencer 2004

The Armfield and Spencer study published in 2004 supports a mere delay. It found an apparent benefit before the age of 12, but no benefit thereafter. Moreover, these researchers have since been found in possession of data that showed a 2 year delay in eruption between fluoridated and unfluoridated communities in Australia.

(g) Demonstration of eruption delay impacts on data

The following chart shows how the false impression of benefit can be given by a delay of 1 year. Representative decay data has been constructed for this demonstration. The same data has been placed in two sets, with one set simply one year later than the other. So there is no difference in tooth decay between the two sets –they are the same data.

The yellow line shows the "benefit" that would be reported by dental researchers. The study would be done at ages up to 12, so the lines would be parallel, as in the UK
study shown earlier. They would not converge until the children were older than in the study.

This pattern is also consistent with the Armfield and Spencer study.

(h) New Zealand Dental Statistics – Ministry of Health

These are the official NZ dental statistics for Year 8 (approx 12 year old) children. They are published without control for socio-economic status, which is the main determinant of oral health (Armfield and Spencer 2004). They also do not allow for delayed tooth eruption (see the York and NHMRC Reviews).

This analysis shows that when adjusting (crudely) for SE status alone the claimed benefit of 30% (actually only ½ a DMFT) disappears in the high SE group, and largely disappears in the rest of NZ. If the rest of NZ were also adjusted for SE status, it is highly likely that even this reduced apparent benefit would disappear.

This shows that the benefit claimed by fluoridation promoters on these figures is an illusion – the difference is due to the higher average SE status of fluoridated communities – mainly large cities.

<table>
<thead>
<tr>
<th>2008</th>
<th>% caries-free</th>
<th>DMFT</th>
<th>benefit</th>
<th>benefit%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>non-F</td>
<td>F</td>
<td>non-F</td>
</tr>
<tr>
<td>High SE</td>
<td>62%</td>
<td>63%</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>Rest of NZ</td>
<td>45%</td>
<td>44%</td>
<td>1.65</td>
<td>1.74</td>
</tr>
<tr>
<td>Combined (false impression)</td>
<td>56%</td>
<td>45%</td>
<td>1.17</td>
<td>1.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2009</th>
<th>% caries-free</th>
<th>DMFT</th>
<th>benefit</th>
<th>benefit%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>non-F</td>
<td>F</td>
<td>non-F</td>
</tr>
<tr>
<td>High SE</td>
<td>59%</td>
<td>57%</td>
<td>1.02</td>
<td>1.04</td>
</tr>
<tr>
<td>Rest of NZ</td>
<td>49%</td>
<td>46%</td>
<td>1.47</td>
<td>1.67</td>
</tr>
<tr>
<td>Combined (false impression)</td>
<td>56%</td>
<td>47%</td>
<td>1.16</td>
<td>1.63</td>
</tr>
</tbody>
</table>
(i) Decay Increasing in Fluoridated Communities

It is also interesting to note that the incidence of tooth decay has been slowly increasing in fluoridated communities in NZ, but decreasing in unfluoridated communities. The NFIS has been unable to explain this:

Note that the difference between the two groups has not been adjusted for socioeconomic status or delayed decay, hence cannot be claimed as demonstrating an overall benefit from fluoridation.

4 Fluoridation and Adults

Promoters cite Griffin 2007 as proof of benefit to adults. This is incorrect. Griffin’s opening statement is:

"To date, no systematic reviews have found fluoride to be effective in preventing dental caries in adults."

According to a 2001 review by the Ontario Ministry of Health and Long Term Care (Locker 2001), "The absence of adults from water fluoridation studies is difficult to...

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explain... Whatever the reason, it must be regarded as a major limitation in the research effort to date."

That is the current position: there is no reliable evidence that fluoridation benefits adults. In fact there are recent studies that show clearly there is no benefit.

Australian research published in March 2013 suggests there is a benefit of 1 filling by age 45, but it is unclear that this is due to fluoridation rather than confounding factors, or that it is statistically significant. This study is discussed below.

(a) Griffin 2007

Griffin is not research: it is a review of research. But only research published in English. It is a literature review, not a systematic review, hence fails to meet Ministry of Health's specifications. Virtually all of the studies were published before the York Review, yet the York reliability rating is not quoted for any study. Neither does this review include the two studies from 2006 and 2007 that specifically found no benefit to adults from fluoridation, discussed below.

A representative of the new Ministry of Health-funded lobby group the NFIS (National Fluoridation Information Service) claimed in May 2011 that Griffin showed a 27% benefit to adults from water fluoridation. However Griffin does not claim this. Griffin stated that there was seemingly a reduction of about 1/2 a DMFS per year from three sources of fluoride:

1. Water
2. Toothpaste
3. Professionally applied lacquers.

Griffin then stated that water fluoridation accounted for 27% of this total; NOT a 27% reduction in decay. If, for example, this 1/2 DMFS was a 30% overall reduction in decay (we do not know as Griffin does not state this, but this is the general claim for 12 year olds in NZ upon raw school dental data, not adjusted for socio-economic status), the water fluoridation component would amount to 8.1% (30% * 27%).

But let us also do a reality check. Half a DMFS per year is 10 DMFS (mainly fillings) over 20 years. But if this is a saving of between 20% and 50% (say), there must be between 1 and 2.5 DMFS per year total. In 20 years (say from age 18 to 38) this is between 20 and 50 fillings! And between 40 and 100 by the age of 58! There are normally 128 tooth surfaces in the mouth. So even the claimed total benefit is simply not credible.

Regarding credibility, Griffin's opening statement at page 410 is:

"To date, no systematic reviews have found fluoride to be effective in preventing dental caries in adults."

A systematic review looks at the reliability of the research before using it. Griffin did not assess reliability - she just quoted the figures. In the case of Hunt Elderidge and Beck, the original research stated that although there were numerically less caries in
the fluoridated subjects, this was within the margin of error - not statistically significant. But Griffin incorporates them anyway, and reports them as significant.

Then at pages 413 and 414 Griffin states:

"One limitation of this review is the quality and the quantity of studies on fluoride effectiveness among adults."

"Because of the paucity of studies, we were not able to exclude studies without blind outcome assessment."

"There is a clear need for further well designed studies on the effectiveness of fluoride among adults."

This is consistent with the York Review finding that there is no reliable evidence to support claims for fluoridation, and that better studies are required.

The studies are old (only 4 post 1979). They include Hunt, Elderidge and Beck as discussed below. They include Burt and Eklund, which compared communities with 3.5 ppm fluoride with communities with 0.7 ppm and is irrelevant to fluoridation, as discussed below.

The study was funded by the Centers for Disease Control (CDC) – one of the two main US political promoters of fluoridation. This was at a time when people were asking "If fluoridation helps developing teeth in children, why are we giving it to adults?" The CDC needed an answer. It is obvious that this shoddy review was commissioned by the CDC specifically as ammunition for the fluoridation lobby, just as the tobacco companies commissioned studies "proving" smoking was "safe".

This is a classic example of the observation made in the British Medical Journal in 2005: that the fluoridation lobby selectively quotes unreliable research to support its position.

(b) Maupomé 2007

In 2007, this important study was published which sheds light on whether fluoridated water is effective at preventing tooth decay in adult populations. Despite a press release to the contrary, the study indicates very little, if any, benefit.

To assess fluoridation's effectiveness, the study examined the dental treatment costs accrued over 5 years by 51,683 members from an HMO. The HMO members, including both adults and children, lived in fluoridated and non-fluoridated communities of 3 separate regions in the Northwest. The authors, a team of pro-fluoridation researchers, state that the study shows a "small" benefit from fluoridated water which "may" have led to some cost-savings. A close inspection of their data, however, shows that this "small benefit" -- if it even exists -- was very small indeed.
For example, in the largest region examined in the study, representing over 75% of the HMO members surveyed (the Portland metro area of Oregon), fewer children and adults in the non-fluoridated areas required treatment than children and adults in the fluoridated areas. Moreover, the children and adults in the non-fluoridated area who sought treatment accrued lower total costs over the 5-year period than those in the fluoridated area. As noted by the authors, the Portland metro had lower treatment costs for the non-fluoridated area..."

These findings from the Portland region are remarkable: after all, one of the most-frequently cited claims by fluoridation proponents is that every $1 spent on fluoridated water saves $80 in dental bills. In this study, the dental care costs in the largest region surveyed were lower in the areas without water fluoridation.

Even among the smaller regions in the study (Marion County, Oregon and Clark County, Washington), which produced more favorable results for the fluoridated areas, the results were still inconsistent and the benefits marginal. As the authors admit, "the effect we observed was generally small."

One of the reasons given by the authors for why the benefit was small and inconsistent was that the population being studied was insured and had ready access to dental care and preventive procedures. However, a separate study by a University of Michigan research team (Burt, 2006) suggests that water fluoridation is equally ineffective in low-income areas as well.

(b) Burt et al. 2006

This study examined a group of 800 low-income African American adults living in Detroit. Despite the fact that Detroit has been fluoridated since 1967, the authors found that tooth decay was "severe" and "extensive", with tooth decay rates reaching as high as 99.8% for individuals aged 14 to 35 years.

What makes this Detroit study particularly interesting, is that, unlike the vast majority of studies investigating fluoridation's effectiveness, the authors actually assessed the quantity of fluoridated tap water consumed by each individual. When they then compared the quantity of fluoridated water consumed with the rate of tooth decay, they found no relationship. In other words, ingestion of fluoridated tap water for up to 4 decades did nothing to produce better teeth in this disadvantaged population.

(d) Earlier Studies Quoted by the NZ Ministry of Health
The Ministry of Health quotes 3 studies:

- Thompson, 1997
- Burt, Ismail and Eckland, 1986
- Hunt Elderidge and Beck, 1989
Yet as we will see, not one of these studies supports the Ministry’s position, in fact the last one shows, if anything, the opposite.

(i) Thompson 1997
(W.M. Thompson 1997: publication for the National Advisory Committee on Health and Disability entitled "Preventive Dental Strategies for Older Populations")

Thompson did no research and simply quotes the earlier study (Burt, Ismail and Eckland, 1986). So Thompson is not an independent authority at all.

(ii) Burt and Eklund

This study did not look at low fluoride communities – it compared a very high fluoride community (3.5 ppm) with a medium fluoride community (0.7 ppm). 3.5 ppm is enough for topical benefit (2ppm threshold). As we know from Arends’ study in 1989, 2ppm or higher is enough for topical benefit. So this study falls into the same error as the original proponents 50 years earlier. It is scientifically invalid to simply extrapolate a straight line back to low fluoride levels with this knowledge: the study proves nothing.

(iii) Hunt, Elderidge, and Beck 1989

This study acknowledged that the number of subjects was too small and the results were not statistically significant, except one.

That conclusion was that adults received no benefit from 30 years of continuous fluoridation. (Specifically the fluoridated and non-fluoridated subjects had the same levels of decay at the beginning of the study {after 40 years of high fluoride exposure in some instances}). With more than 30 years exposure, it concluded that there was on average ½ a cavity less in the fluoridated communities.

In fact this found (at the start of the study) no difference in decay rates after 30 to 40 years of exposure to fluoride at 1 ppm. At the end of the 18 month study it claimed an apparent minor benefit but noted that it had not considered use of fluoride toothpaste, other dental treatments, or any confounding factors of any kind. The report states:

"information on other sources of fluoride, such as fluoride toothpastes and mouthrineses, was not collected. Thus it is possible that the differences in caries incidence were due to other sources of fluoride."
It also failed to note that claiming a benefit for, say, 32 yr olds after the study, but none for 32 yr olds at the start of the study, was self contradictory.

As an interesting aside, the study notes that its results "indicate that the topical effect of currently consumed fluoridated water was not sufficient by itself to significantly reduce caries."

The obvious question is "why would anyone take a known poison so that after 30 or 40 years they may have a 50/50 chance of saving one filling?!"

**Fluoridated Water for Adults: Very Little, if any, Benefit**

In 2007, an important study was published which sheds light on whether fluoridated water is effective at preventing tooth decay in adult populations (9a). Despite a recent press release to the contrary, the study indicates very little, if any, benefit.

To assess fluoridation’s effectiveness, the study examined the dental treatment costs accrued over 5 years by 51,683 members from an HMO. The HMO members, including both adults and children, lived in fluoridated and non-fluoridated communities of 3 separate regions in the Northwest. The authors, a team of pro-flouridation researchers, state that the study shows a "small" benefit from fluoridated water which "may" have led to some cost-savings. A close inspection of their data, however, shows that this "small benefit" -- if it even exists -- was very small indeed.

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These findings from the Portland region are remarkable: after all, one of the most-frequently cited claims by fluoridation proponents is that every $1 spent on fluoridated water saves $80 in dental bills. In this study, the dental care costs in the largest region surveyed were lower in the areas without water fluoridation.

Even among the smaller regions in the study (Marion County, Oregon and Clark County, Washington), which produced more favorable results for the fluoridated areas, the results were still inconsistent and the benefits marginal. As the authors admit, "the effect we observed was generally small."

One of the reasons given by the authors for why the benefit was small and inconsistent was that the population being studied was insured and had ready access to dental care and preventive procedures. However, a separate study by a University of Michigan research team suggests that water fluoridation is equally ineffective in low-income areas as well (9b). The study examined a group of 800 low-income African American adults living in Detroit. Despite the fact that Detroit has been fluoridated since 1967, the authors found that tooth decay was "severe" and
"extensive", with tooth decay rates reaching as high as 99.8% for individuals aged 14 to 35 years.

What makes this Detroit study particularly interesting, is that -- unlike the vast majority of studies investigating fluoridation’s effectiveness -- the authors actually assessed the quantity of fluoridated tap water consumed by each individual. When they then compared the quantity of fluoridated water consumed with the rate of tooth decay, they found no relationship. In other words, ingestion of fluoridated tap water for up to 4 decades did nothing to produce better teeth in this disadvantaged population.


(e) Australian Research 2013

Slade G D, Sanders A E, Do L, Roberts-Thomson K, Spencer A J -Effects of Fluoridated Drinking Water on Dental caries in Australian Adults"  *J Dent Res*  online 1 March 2013

**Summary**

Although the study is reasonably well conducted, it is quite possible that the apparent benefit is due to confounding factors that have not been adequately allowed for. The apparent benefit is only one filling after 45 years exposure. It is not clear that this is statistically significant. Ultimately this is only one study amongst many that have failed to show a statistically significant benefit to adults.

**Discussion**

A quick read through shows
1. It’s an ecological study, rather than the golden standard randomized, double blinded clinical trial.
2. They used questionnaires to ask people if they 'remembered' where they lived their whole lives. Canadians, Americans and New Zealanders were assumed to be exposed to 0.5 ppm across the board no matter what. There are lots of flaws in this approach.
3. They used a very crude formula to figure out fluoride exposure-years (like cigarette pack years)
4. They clearly showed caries rates declined in Australia almost equally in all groups (not much difference at all between low exposure versus high exposure to fluoridated water)
5. They counted lost teeth from gum disease and finally, but most importantly
6. The difference between the DMFT scores for those assumed to have had high exposure to fluoridated water compared and those who had low fluoridated water exposure was only 1.14. The significant level was P <0.02. Not very convincing.
This is more than what they found in other Australian studies by the same group (Spencer 1996, Armfield and Spencer, 2004) for younger cohorts.....but not so surprising since
a) people continue to have more fillings placed as they get older (whether they need them or not is sometimes debatable)
b) the more fillings you have (or the more dental decay you have) the greater number of tooth surfaces that apparently benefit if the percentage difference resulting from fluoridation is consistent.

Rough calculations based on current known rates of moderate to severe fluorosis caused by fluoridation in the US, it will cost much more to treat the fluorosis caused by fluoridation than the fillings supposedly saved by it. (Note: dental fluorosis does not reach "severe" level in NZ, though does reach "moderate" level)
In fact using realistic estimates of the cost of fluoridation the savings in dental costs are actually less than the total costs of fluoridation (based on the 1.14 fillings saved over a lifetime of fluoridation)

If anything this research shows that fluoridation is not cost effective.

5 Fluoridation and the Poor

The York Review could find no reliable evidence that fluoridate water preferentially benefited the poor. Similarly, Armfield and Spencer 2004 found that the main determinant of oral health was socio-economic status regardless of fluoridation status.

ESR 1999

ESR claim: "The table shows that, generally, fluoridated water has greater benefits for children attending schools whose pupils are drawn from less privileged areas." However, consistent with 50 years of research, and particularly Armfield and Spencer 2004, the apparent "benefit" disappears as the child enters the teens (about age 14 if this data is extrapolated).
Data supplied by the Hawke’s Bay District Health Board

Year 8 Pacific Island children: Less decay in unfluoridated community: no "social equity" from fluoridation

Year 8 Maori children: Similar decay in both communities: no "social equity" from fluoridation

Added risk to the poor
In fact the poor are most at risk from fluoridation, as poor diet, especially if low in calcium and magnesium, offers less protection to fluoride’s inherent toxicity.

Earlier this year Dr Andrew Young, black civil rights leader, former close associate of the late Martin Luther King Jr., former US ambassador to the UN, and former Governor of Atlanta, awarded the French Congressional medal of Honour amongst many other decorations for his work, called for an end to fluoridation due to the disproportionate harm it inflicts upon African-Americans and Hispanics.

His reasons apply equally to Maori and Pacific Peoples – higher diabetes rates, higher incidence of kidney dysfunction (both high risk groups identified by the US NRC Review), and lower Vitamin D levels due to darker skin pigmentation (resulting in poorer calcium metabolism, important for counteracting fluoride’s inherent toxicity.

The particular impact on non-whites was a key finding in relation to premature births, discussed elsewhere in this paper.

6 Ending fluoridation

The following chart shows the decline in tooth decay in Timaru following cessation of fluoridation in 1985. The long flat section reflects the fact that we do not have official data for those years. However the total movement over the period shown in the graph is accurate.

When asked to explain this to the Policy and Strategy Committee, Ministry of Health Chief Dental Officer Dr Robyn Haisman-Welsh said it was because Timaru was a wealthy area.
Even if this were true, it would only have had an impact if Timaru’s socioeconomic status had increased dramatically, overnight, in 1985.

But the Ministry’s own published deprivation map shows it is untrue – Timaru is in the lower half of the SES scale.

The statistics as provided to Imelda Hitchcock, with original references.

<table>
<thead>
<tr>
<th>Year</th>
<th>MFT</th>
<th>CF%</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>3.75</td>
<td>15.04%</td>
<td>DOH from M.B.Henderson</td>
</tr>
<tr>
<td>1985</td>
<td>3.30</td>
<td>16.13%</td>
<td>&quot;</td>
</tr>
<tr>
<td>1987</td>
<td>2.96</td>
<td>21.30%</td>
<td>Paper by Dr John Colquhoun - published in Australia and NZ Public Health</td>
</tr>
<tr>
<td>1988</td>
<td>2.59</td>
<td>25.69%</td>
<td>MOH Statistics</td>
</tr>
<tr>
<td>1989</td>
<td>2.23</td>
<td>31.05%</td>
<td>Alan Roddick, Primary Health</td>
</tr>
<tr>
<td>2002</td>
<td>2.09</td>
<td>31%</td>
<td>Sth. Canterbury School Dental Service Data - supplied by Michele Keggenhoff Communication Advisor, SCDHB</td>
</tr>
<tr>
<td>2003</td>
<td>1.63</td>
<td>42%</td>
<td>&quot;</td>
</tr>
<tr>
<td>2004</td>
<td>1.63</td>
<td>41.98%</td>
<td>&quot;</td>
</tr>
<tr>
<td>2005</td>
<td>1.80</td>
<td>41.90%</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
"No increase in caries (cavities) was found in Kuopio (Finland) 3 years after the discontinuation of water fluoridation," according to Caries Research.

Seven years after fluoridation ended in LaSalud, Cuba, cavities remained low in 6 to 9 year olds, decreased in 10 to 11 year-olds, significantly decreased in 12 to 13 year olds, while caries-free children increased dramatically, reports Caries Research.

East German scientists report, "following the cessation of water fluoridation in the cities Chemnitz and Plauen, a significant fall in caries prevalence was observed," according to Community Dentistry and Oral Epidemiology.

Not only did decay rates remain stable during an 11-month fluoridation break in Durham, NC, between September, 1990, and August, 1991 but dental fluorosis declined in children born during that period, according to the Journal of Dental Research.

In British Columbia, Canada, "the prevalence of caries decreased over time in the fluoridation-ended community while remaining unchanged in the fluoridated community," reported in Community Dentistry and Oral Epidemiology.

In 1973, the Dutch town of Tiel stopped fluoridation. Researchers counted drilled, missing, and filled tooth surfaces (DMFS) of Tiel's 15-year olds, then collected identical data from never-fluoridated Culemborg. DMFS initially increased in Tiel then dipped to 11% of baseline from 1968/69 to 1987/88 while never-fluoridated Culemborg's 15-year-olds had 72% less cavities over the same period, reports Caries Research.

7 Costs of Fluoridation
It is often claimed that for every dollar spent on water fluoridation, $38 are saved in dental treatment. However this claim has yet to be demonstrated. In the US and Canada more money is spent treating dental fluorosis than on treating decay.

Further, the claim is based only on the chemical costs of fluoridation. These are artificially low because a contaminated waste grade of fluoride (called
—water treatment grade’) is bought cheaply as hazardous waste from superphosphate manufacturers. If an appropriately pure grade were used the cost would be much higher.

Other costs that should be considered under a standard economics analysis include:

- Ongoing lobbying and campaigning costs
- NFIS 1.2 m
- Former HVDHB contracts $330K and $200K
- Training public health staff
- Training public health staff in arguing against opponents
- Employment costs re handling hazardous materials
- More rapid deterioration of water pipes
- Ministry staff costs
- Research costs
- Costs of dental fluorosis
- Costs of increased —arthritis"
- Costs of increased morbidity and mortality from increased premature birth rates
- Costs of increased cardiovascular disease
- Costs of fluoridation equipment (350K in Kaitaia and Kaikohe)
- Cost to individuals avoiding fluoridated water (filters etc)

8  Cost Effectiveness of Using the Water Supply for Fluoride Delivery

This calculation shows the amount spent on water fluoridation by Wellington Regional Council, and how much of it is actually consumed by residents

—Imecent years our annual water supply has typically varied between about 55-56,000 million litres, or just over 1,000 million litres in an average week. If Wellington’s Westpac Stadium were a reservoir, this weekly volume would fill it completely.
Our supply currently serves a resident population of around 380,000, so on average we provide about 400 litres per resident each day, or four bathtubs each. Not all of this water is used by individuals at home. Businesses, industry, schools, hospitals, councils etc all use water too.” [Emphasis mine]

BREAKING DOWN WATER USE AND THE COST OF FLUORIDATION
water usage 400L / day / person
http://www.wellington.govt.nz/services/watersupply/
recommended drinking water 2.5L / day
http://www.mayoclinic.com/health/water/NU00283
water down drain 397.5L / day
% drinking of total water usage 0.625% of all water consumed is drunk
99.375% of water supplied goes down the drain / into the environment. 
fluoridating water cost: $ 195 000.00 / year http://www.gw.govt.nz/fluoride-2/ 
$ spent on fluoridating water that is drunk (0.625%): $ 1 218.75 / year 
$ spent on fluoridating water that is not drunk (99.375%) $ 193 781.25 / year 

**ECONOMIC CONCLUSION**
The Greater Wellington City Council website states that the water supply is fluoridated for "good dental health." Yet less than one percent of the fluoridated water supply is actually ingested, while the other 99.375% is used for cleaning, bathing, watering the garden etc.

Therefore, of the $195,000 dedicated to the "good dental health" of Wellington residents, **only $1218.75 is actually being applied to their teeth**, which means **$193,781.25 is literally being poured down the drain every year,**

This does not preclude the possibility that, if fluoridation did actually reduce tooth decay, which remains unproven, even with this waste it might still be cost-effective. But a more thorough economic analysis than is currently available would be required to demonstrate this. Promoters claim that every dollar spent on fluoridation (including that flushed down the drain) saves $38 in tooth decay. But there is no sound economic analysis backing up this claim. In fact in the US promoters seem to be resiling from this claimed saving.

**D THE SAFETY OR DANGER OF FLUORIDATION**

**Attachments**

Kathleen Theissen, NRC Panel member, on the NRC Review

Developmental Fluoride Toxicity – Harvard School of Public Health

According to the US Environmental Protection Association, as at 2002 no human health safety studies had been conducted on silicofluorides used in fluoridation.²⁵

Fluoridation promoters claim that the fluoride ion is the same no matter where it comes from, so there is no difference between silicofluorides and calcium or sodium fluoride. This is completely misleading.

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²⁵ Request for Assistance Measurement Of Fluorosilicates In Drinking Water 
April 25 2002. Full text at  
That silicofluorides do not completely dissociate in water was shown by Crosby in 1969. Crosby used two measures, showing 87% and 95% dissociation respectively. His abstract interprets this as “at least 95%”, for reasons that are unclear. Crosby is constantly misquoted as proving the dissociation was 100%, which is incorrect. In my research, every other author cited as authority on this point has ultimately (falsely) relied on Crosby, either directly or indirectly through their references. Some also quote Urbansky and Schock, 2000, but this was not research – it was a theoretical “opinion piece” commissioned by the US Government (for whom Urbansky worked) as “damage control” following release of Masters and Coplan’s research in 1999.

More importantly, all silicofluoride breakdown components remain available for chemical reaction, so whether the substance has fully ionised or not is in this respect irrelevant.

Further, when silicofluorides are put in acidic conditions, such as stomach acid, they tend to return to the molecular form (the dissociation constant shifts).

According to WHO (2006) 40% of fluoride is absorbed through the stomach as molecular hydrofluoric acid.

Research has shown that silicofluorides have some different biological effects on humans than either calcium fluoride or sodium fluoride. This relates to inhibition of the enzyme acetylcholinesterase, and the absorption of lead.

1 Dose v Concentration

The issue of toxicity is related to dose. The No Observed Adverse Effect Level used to be set at 3 mg/day. This was increased without any scientific basis to 10 mg/day. In fact crippling skeletal fluorosis is observed below this level, and many studies on IQ and hearty disease show adverse effects below this level.

26 Crosby NT; "Equilibria of Fluosilicate Solutions with Special Reference to The Fluoridation of Public Water Supplies"; J Appl Chem; v19; pp 100-102, 1969.
The increase was most likely no more than a political move to retain fluoridation policy in the face of increasing exposure to fluoride, above the earlier upper limit.

The NRC Review identified a number of subgroups with higher than normal water consumption, and therefore at heightened risk:

- Diabetics
- Athletes
- Outdoor workers
- Bottle-fed infants

It also identified those with kidney dysfunction as being more vulnerable due to reduced ability to excrete fluoride.

The 0.7ppm level is set on an assumed consumption of 1.5 litres of water per day.

Australian miners consume up to 12 litres of water a day.
An endurance cyclist could well consume 8 litres in a race. 30
A golfer could consume 3 litres in a round of golf. 31

Beverages, including organic beverages, may be made with fluoridated water, without the consumer's knowledge, 32 as may processed foods.

In short, there is no control over dose, hence no control over risk from fluoridation.

(a) Skin absorption

Fluoride is also absorbed through the skin while showering or bathing. This can be more than the assumed total exposure on which fluoridation was based (1 – 1.5 mg/day) 33

―Most are surprised to learn that waterborne chemicals, including fluorides, are readily absorbed into the body from showering or bathing 1. In fact, these chemicals are actually more dangerous when absorbed through the skin, for in this manner they enter the bloodstream more easily, bypassing the gut where they would bind with minerals from food, thus diminishing their harmful effects.‖

30 Personal communication by an endurance cyclist
31 Personal discussion with golfers at the Boulcott Golf Club, Lower Hutt.
32 Advice from Coca Cola Amaltil, Phoenix Organic Beverages.
33 Barry Grove, Drinking Ourselves to Death?, Newleaf, 2001, p 275. cited at http://www.healthcarealternatives.net/removingfluoride.htm#2
It is well documented that environmental contaminants such as fluorides are absorbed readily both through the skin and by inhalation ...

Studies by Drs. H.S. Brown, D.R. Bishop and C.A. Rowan in the early 1980s demonstrated that an average of 64% of the total dose of waterborne contaminants, such as fluoride, are absorbed through the skin. (*American Journal of Public Health* 1984; 74: 479-84) — Fluoride: Drinking Ourselves to Death, Barry Groves, pp. 275-265

...dermal absorption through showering and bathing may be the primary means of fluoride intake...roughly 2/3 of fluoride absorbed in a person’s body is through showering and bathing (assuming the person is serviced by a water system that fluoridates their water)...

George Glasser, an American investigative journalist, did research into fluoride and among his conclusions and findings on the dangers of fluoride are that the EPA found that more chemical contaminants are absorbed through the skin than through ingestion. He also mentions a University of Pittsburgh study containing the same conclusion....

...about 20-50 percent of chemical contaminants are metabolized when foods or beverages are consumed. With dermal exposure and inhalation, however, virtually 100 percent of the contaminants are absorbed directly into the bloodstream....In 1997, the EPA concluded that a person can absorb more contaminants from bathing and showering than from drinking polluted water.

Children are most at risk. Children's bath times may range from 45 minutes to two hours. As the EPA acknowledged in a June 30, 1998 report, "Children have a greater surface-area-to-body-weight ratio than adults, which may lead to increased dermal absorption."

2 Neurotoxicity

(a) Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis 2012

The NFIS, if it addresses this paper, will no doubt focus on the identified shortcomings so as to ignore the overall findings. For that reason I attach the full paper for your reference.

34 http://www.purewatergazette.net/fluorideandphosphate.htm
36 Anna L Choi. Guifan Sun, Ying Zhang, Philippe Grandjean Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis "Environmental Health Perspectives, Online 20 July 2102 http://dx.doi.org/10.1289/ehp.1104912
Fluoride readily crosses the placenta. (ATSDR 2003) Fluoride exposure to the developing brain, which is much more susceptible to injury caused by toxicants than is the mature brain, may possibly lead to damage of a permanent nature (US EPA 2011).

The review more systematically addresses study selection and exclusion information, and is overall more comprehensive than previous reviews.

As noted by the NRC 2006, assessments of fluoride safety have relied on incomplete information on potential risks. In regard to developmental neurotoxicity, much information has been published but these have not been available to most expert committees.

―The results suggest that fluoride may be a developmental neurotoxicant that affects brain development at exposures much below those that can cause toxicity in adults.‖

―In conclusion, our results support the possibility of adverse effects of fluoride exposures on children’s neurodevelopment. Future research should formally evaluate dose-response relations based on individual-level measures of exposure over time, including more precise prenatal exposure assessment and more extensive standardised measures of neurobehavioural performance.‖

―The estimated decrease in average IQ associated with fluoride … may seem small and may be within the measurement error of IQ testing. However, as research on other neurotoxicants has shown, a shift to the left of IQ distributions in a population will have substantial impacts, especially among those in the high and low ranges (Bellinger 2007)‖

The review found a correlation between fluoride exposure and lowered IQ independent of other potential causes such as arsenic and low iodine. It further found that, from the geographical distribution of the studies and the local mineral content, it was unlikely that the effect was due to neurotoxicants other than fluoride.

―Although the studies were generally of insufficient quality, the consistency of their findings adds support to existing evidence of fluoride-associated cognitive deficits, and suggests that potential developmental neurotoxicity of fluoride should be a high priority for research.‖

Professor Grandjean, head of the Harvard Public Health School and leading researcher in developmental neurotoxicology said this:
On average, the children with higher fluoride exposure showed poorer intelligence test performance. The high exposures generally exceeded the concentrations normally occurring in fluoridated drinking water, but only 4 of 27 studies reached an excess of 10-fold, and clear differences were found also at much lower exposures.

Chemical brain drain should not be disregarded. The average IQ deficit in children exposed to increased levels of fluoride in drinking water was found to correspond to about 7 points – a sizable difference. To what extent this risk applies to [water fluoridation at 0.7 to 1 ppm] is uncertain, but definitely deserves concern.

The key issue of course is not concentration but daily dose.

(i) **US Government Data on Mental Retardation and Fluoridation**

These findings are supported by US Government data published by the Centers for Disease Control and Prevention in 1993.37 These data show a clear correlation between the rate of mental retardation per capita in children, and the percentage of the population exposed to water fluoridation (0.7 to 1.2 ppm in the US).

Vertical axis: Mental retardation prevalence for children (6-17 years old) per 1,000 population in 1993.

Horizontal Axis: Water fluoridation rates in 1992

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37 Published at http://photos.oregonlive.com/photogallery/2012/10/water_fluoridation_and_mental.html
This is a literature review. The review is helpful in canvassing literature on fluoride's neurotoxicity. The review's focus is on water fluoride levels higher than that used in water fluoridation. However the issue with fluoride toxicity is not the level in water but the total daily intake. Levels at which fluoride neurotoxicity is shown by the research canvassed in this review are reached by some members of communities fluoridated at 0.7 to 1 ppm. The studies do not address the proportion of the population with heightened sensitivity to fluoride toxicity.

The review identifies the following research findings:

- "Various studies, both clinical and experimental, have reported that Fluoride causes alterations on the morphology and biochemistry brain, affecting neurological development of individuals and, therefore,
functions related to cognitive processes, such as learning and memory.

- "Fluoride is capable of crossing the blood-brain barrier, which may cause biochemical and functional changes in the nervous system during pregnancy. Since the Fluoride accumulates in brain tissue before birth it has been reported that exposure of the embryo to Fluoride during pregnancy is associated with impaired learning."

- Research results suggest that the accumulation of Fluoride in the tissue can disrupt brain neurotransmitters synthesis and nerve cell receptors, have a specific effect on protein synthesis in the brain, leading degenerative changes in neurons and changes in the cerebellar cortex. These changes indicate that Fluoride can slow growth and cell division in the cortex, and that the smaller number of mitochondria, microtubules and synaptic vesicles in the terminal may decrease efficacy between the neural connections, produce abnormal operation, and influence synaptic development during postnatal life.

The study recommends that people in communities with more than 0.7ppm fluoride in the water avoid all other sources of fluoride, including toothpaste. Even if all New Zealand adopted a maximum of 0.7ppm, this would allow ZERO margin of safety. Current official standards for "safe" fluoride exposure use a zero margin of safety on the (false) claim that dental fluorosis is only cosmetic. That argument cannot apply in the case of neurotoxicity, hence the usual safety margin of 10 would be appropriate (i.e. less than 0.1ppm).

Finally, this is not systematic review, hence the quality of research canvassed is not assessed. However, the research has been published in peer-reviewed journals of international standing, mostly since 2002, and all since 1992. Today's methodology is generally more sound than that of older studies.

(c) Mullinex et al 1995

This study was conducted on rats, using a computerized observational technology to assess neurological damage, avoiding observer bias and fatigue.

Although the levels of fluoride in the water were high, the blood plasma levels of fluoride were in the range experienced in fluoridated communities. Compared with humans, rats drink very little water, absorb less fluoride, and are more resistant to neurotoxicants.

Her findings clearly detailed the developmental effects of fluoride, pre- and postnatal. Doses administered before birth produced marked hyperactivity in offspring. Postnatal administration caused the infant rats to exhibit what Dr.

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Mullenix calls the "couch potato syndrome"—a malaise or absence of initiative and activity.

—This study demonstrates a link between certain fluoride exposures and behavioral disruption in the rat. The effect on behavior varied with the timing of exposure during CNS development. Behavioral changes common to weanling and adult exposures were different from those after prenatal exposures... Experience with other developmental neurotoxicants prompts expectations that changes in behavioral function will be comparable across species, especially humans and rats... [A] generic behavioral pattern disruption as found in this rat study can be indicative of a potential for motor dysfunction, IQ deficits and/or learning disabilities in humans.”

(d) Guan et al 2004

This research was conducted by the world’s leading brain research team, at the Swedish Karolinska Institute.

The study is the latest by a team of Chinese and Swedish scientists, members of which have been researching the impact of fluoride on brain for the past 8 years.

The team, headed up by neurotoxicologist Dr. Zhizhong Guan from the, has probably investigated the impact of fluoride on brain more thoroughly than any other team in the world. Dr. Guan himself has researched the issue since as far back as 1986, although most of his research on the issue has been published since 1997 (see below).

The 2004 study investigates an important finding they first reported in 2002: namely, that rats drinking fluoride in water for 7 months had a decrease in —nicotinic acetylcholine receptors", or -nAChRs", in their brains.

—We have detected the alterations of nicotinic acetylcholine receptors (nAChRs) in rat brains and PC12 cells affected by fluoride toxicity... [O]xidative stress, including protein oxidation of the receptors and lipid peroxidation in cellular membrane, might be a mechanism of the deficit of the receptors."

Rats drinking fluoride in water for 7 months had a decrease in

nicotinic acetylcholine receptors”, or ”nAChRs”, in their brains. The blood fluoride levels found in rats at the exposures given are also found in humans in fluoridated communities, and in children if they swallow fluoride toothpaste.

The association with Central Nervous System disorders has been researched by Dr. Agneta Nordberg, a Swedish neurotoxicologist and expert on nAChRs: “The nAChRs in the brain are important for functional processes, including cognitive and memory functions... The nAChRs are found to be involved in a complex range of central nervous system disorders including Alzheimer’s disease (AD), Parkinson’s disease, schizophrenia, Tourette’s syndrome, anxiety, depression, and epilepsy.”

The link with Alzheimers’ was earlier reported by Nordberg (Ref: Nordberg. *Biological Psychiatry* 2001; vol. 49; pp. 200-10.)

**The Potential Implications of Reduced nAChRs in the Brain**

The potential implications of the Guan team’s finding can be gleaned from a recent review by Dr. Agneta Nordberg, a Swedish neurotoxicologist and expert on nAChRs.

According to Nordberg (who is now working with Dr. Guan on his fluoride/brain research):

—$$\text{The neuronal nicotinic acetylcholine receptors (nAChRs) in the brain are important for functional processes, including cognitive and memory functions... The nAChRs are found to be involved in a complex range of central nervous system disorders including Alzheimer’s disease (AD), Parkinson’s disease, schizophrenia, Tourette’s syndrome, anxiety, depression, and epilepsy. The exact role of nAChRs and their full potential as a therapeutic target in these diseases have yet to be clarified.}$$

In regards to the relationship between decreased nAChRs and alzheimers disease, Nordberg writes:

—$$\text{A consistent, significant loss of nAChRs has been observed in cortical autopsy brain tissue from [alzheimers] patients relative to age-matched healthy subjects. More recently, we have found that the nAChR deficits in [alzheimers] brains probably represent an early phenomenon in the course of the disease, which can be detected in vivo by positron emission tomography.}$$ (Ref: Nordberg. *Biological Psychiatry* 2001; vol. 49; pp. 200-10.)
In 2002, when it was first reported (in the journal *Neurotoxicology & Teratology*) that fluoride could decrease nAChRs in rat brain, Dr. Guan, Dr. Nordberg and colleagues stated:

—Since AChRs play major roles in cognitive processes such as learning and memory, the decrease in the number of nAChRs caused by fluoride toxicity may be an important factor in the mechanism of brain dysfunction in the disorder."

In the new 2004 study, Dr. Guan, Dr. Nordberg, and colleagues, report on how fluoride might be causing the reduction in these nAChRs.

Their tentative conclusion is that the reduction is connected to a fluoride-induced increase in oxidative stress. Supporting this conclusion was the finding that pre-treating the rats with anti-oxidants seemed to prevent the reduction in nAChRs caused by fluoride.

The conclusion is also supported by a series of earlier studies from the Guan team which found that oxidative stress plays an important role in fluoride toxicity, not only in the brain, but in the liver and kidney as well.

**Relevance to humans?**

In their studies on fluoride toxicity, Guan and colleagues use 3 groups of rats. 1 group receives no fluoride in their water, 1 group receives 30 ppm fluoride, while 1 group receives 100 ppm fluoride. The duration of the studies is usually 7 months.

Among the 3 groups of rats, Guan has found that – while the damage is consistently greatest in the 100 ppm group – damage also occurs in the 30 ppm group as well. Damage in the 30 ppm group includes increased oxidative stress (as reflected by reduced lipid content) and reductions of some (but not all) nAChRs.

On the face of it, it would seem that rats drinking 30 ppm fluoride in water are receiving roughly 30 times more fluoride than humans drinking fluoridated water (1 ppm). However, upon closer inspection, this assumption does not hold true, because rats are more resistant to fluoride toxicity than humans. The increased resistance of rats’ to fluoride toxicity seems to stem from the ‘reduced intestinal absorption’ of fluoride found in the rat. In other words, when rats ingest fluoride, less of the ingested fluoride actually makes it into their bloodstream. Because of this, rats are known to have far lower levels of fluoride in their blood than humans when consuming the same level of fluoride in water.
Indeed, while Guan and colleagues do not provide data on the level of fluoride in the rats’ blood, the blood levels normally found in rats drinking ~30 ppm fluoride in water (range = ~76-143 ppb) are actually overlapped and exceeded on a chronic basis by a portion of the human population (particularly those with kidney disease) living in fluoridated, and even unfluoridated, areas.

Moreover, the lower range of the levels normally found in rat’s blood drinking 30 ppm fluoride are also reached by young children (albeit for short duration) after ingesting fluoridated toothpaste and/or fluoride supplements.

Animal Studies from Dr. Guan & Colleagues


—Thee findings suggest that selective decreases in the number of nAChRs may play an important role in the mechanism(s) by which fluoride causes dysfunction of the central nervous system.”


—In order to investigate the molecular mechanism(s) underlying brain dysfunction caused by chronic fluorosis, neuronal nicotinic acetylcholine receptors (nAChRs) in the brain of rats receiving either 30 or 100 ppm fluoride in their drinking water for 7 months were analyzed in the present study employing ligand binding and Western blotting... Since nAChRs play major roles in cognitive processes such as learning and memory, the decrease in the number of nAChRs caused by fluoride toxicity may be an important factor in the mechanism of brain dysfunction in the disorder.”

Over uptake of fluoride for a long term could cause potential increase in the level of oxidative stress in the brain tissue.”


- The results demonstrate that the contents of phospholipid and ubiquinone are modified in brains affected by chronic fluorosis and these changes of membrane lipids could be involved in the pathogenesis of this disease.”


- Coenzyme Q content of brain tissue in rats fed with fluorine-containing water decreased at early stage of fluorosis, but increased significantly at late stage. It is speculated that changes in content of coenzyme Q could correlate with changes in free radical levels induced by fluorine.”


- The metabolism of brain phospholipid might be interfered by fluoride accumulated in brain tissue, which is related with the degeneration of neuron. The changes of brain phospholipid could be involved in the pathogenesis of chronic fluorosis.”

Animal Studies from other research teams


—Fluorosis had obvious influence on phospholipid and fatty acid composition in brain cells of rats, and its mechanism might be associated with action of lipid peroxidation, and 0.03 mg/L KI
(potassium iodine) is the optimal concentration for the antagonistic action with this influence from fluorosis.”


-These neurotoxic changes in the brain suggested that there was a direct action of fluoride upon the nerve tissue which was responsible for central nervous system problems such as tremors, seizures, and paralysis indicating brain dysfunction seen at the two highest doses.”


-CONCLUSION: Fluoride may go through the blood-brain barrier and accumulate in rat hippocampus, and inhibit the activity of cholinesterase.”


—Light microscopic study of hippocampal sub-regions demonstrated significant number of degenerated nerve cell bodies in the CA3, CA4 and dentate gyrus(Dg) areas of sodium fluoride administered adult female mice. Ultrastructural studies revealed neurodegenerative characteristics like involution of cell membranes, swelling of mitochondria, clumping of chromatin material etc, can be observed in cell bodies of CA3, CA4 and dentate gyrus (Dg). Fluoride intoxicated animals also performed poorly in motor co-ordination tests and maze tests. Inability to perform well increased with higher fluoride concentration in drinking water.”


-The DNA damage in pallium neurons in rats of the fluoride group was much more serious compared with those of the control
Sodium fluoride could induce DNA damage and apoptosis in rats brain."


"These results suggest that fluoride enhances oxidative stress in the brain, thereby disturbing the antioxidant defense of rats. Increased oxidative stress could be one of the mediating factors in the pathogenesis of fluoride toxicity in the brain."


"Rats exposed to 100 ppm fluoride showed significant neurodegenerative changes in the hippocampus, amygdala, motor cortex, and cerebellum... These histological changes suggest a toxic effect of high-fluoride intake during the early developing stages of life on the growth, differentiation, and subcellular organization of brain cells in rats."


"Administration of sodium fluoride with drinking water produced both behavioural and dental toxicities and not lethality in the present study. A suppression of spontaneous motor activity, a shortening of rota-rod endurance time, a decreased body weight gain and food intake, a suppression of total cholinesterase and acetylcholinesterase activities and dental lesion were observed in test animals."


"The main results showed that the learning capability of mice drinking higher concentration of fluoride presented remarkable deterioration."

—The extent of DNA damage in the fluoride + selenium + zinc group was significantly slighter than that in the fluoride group (P < 0.05). It suggested that fluoride and selenium could induce DNA damage in pallium neural cells of rats respectively.”


—This study therefore shows that both brain and muscle are affected by fluoride with inhibition of some enzymes associated with free-radical metabolism, energy production and transfer, membrane transport, and synaptic transmission, but with an enhanced activity of XOD.”


—There is a tendency for neurone apoptosis in chronic fluorososis in rats. It is most evident with changes in pathology. It is not likely that only one form of neurone damage exist in the process of chronic fluorosis. There are recessive changes and apoptosis in the process at the same time.”


—Results: Learning and memory abilities of high-fluoride exposed groups were significantly lower than that of the control group, while the brain ChE activities of high-fluoride exposed groups were significantly higher. Conclusions: High fluoride concentration in drinking water can decrease the cerebral functions of mice. Fluoride is a neurotoxicant.”

van der Voet GB, et al. (1999). Fluoride enhances the effect of aluminium

-It was concluded that aluminium interferes with the metabolism of the neuronal cytoskeleton and that this interference is potentiated by fluoride."


-The main results are as follows: the learning ability of mice drinking high concentration of fluoride presented remarkable deterioration, the thickness of post-synaptic density (PSD) was decreased, and the width of synaptic cleft was remarkably increased. The results suggested that the impairment on the learning capability induced by fluorosis may be closely related with the pathological changes of synaptic structure in the brain of mice."


-Sodium fluoride treatment suppressed spontaneous motor activity. But no change was observed in the motor coordination of these animals. A suppression of spontaneous motor activity suggests that fluoride has, by a central action, inhibited motivation of these animals to exhibit locomotor behavior."


-While the small amount of AlF in the drinking water of rats required for neurotoxic effects is surprising, perhaps even more surprising are the neurotoxic results of NaF at the dose given in the present study 2.1 ppm... The results of the present study indicate that more intensive neuropathological evaluations of F effects on brain may prove to be of value... In summary, chronic administration of AlF and NaF in the drinking water of rats
resulted in distinct morphological alterations in the brain, including effects on neurons and cerebrovasculature."


"These results indicate that fluoride may penetrate the blood brain barrier, interact with AChE located on cell membranes, and interfere with their physiological functions thus induce the neurotoxicities."


"Neuronal abnormalities were observed in the NaF treated animals- especially in the deeper cell layers... The NaF treatment also produced distortions of cells and, in some rats, cell losses could be demonstrated in particular brain regions. Both AlF3 and NaF induced vascular inclusions, although of a different character...”


"Excessive fluoride intake decreased 5-hydroxy indole acetic acid and increased norepinephrine in rat brain."


"Bioc hemical alterations in the brain produced during experimental fluorosis were studied... The depletion of proteins produced degenerative changes in purkinje c1les of the cerebellar cortex.”

The neurotoxic effect of fluoride on lipid content of brain was assessed in rabbits during experimental fluorosis... **Fluoride exerts an inhibitory effect on the free fatty acids in brain of both sexes.** The relevance of these results in experimental fluorosis is discussed."

### 3 Heart Disease
Li, Yuxin; Berenji, Gholam R.; Shaba, Wisam F.; Tafti, Bashir; Yevdayev, Ella; Dadparvar, Simin — Association of vascular fluoride uptake with vascular calcification and coronary artery disease" *Nuclear Medicine Communications*: January 2012, Volume 33, Issue 1; p 14–20

(a) Abstract

Objective: The feasibility of a fluoride positron emission tomography/computed tomography (PET/CT) scan for imaging atherosclerosis has not been well documented. The purpose of this study was to assess fluoride uptake of vascular calcification in various major arteries, including coronary arteries.

Methods: We retrospectively reviewed the imaging data and cardiovascular history of 61 patients who received whole-body sodium $[^{18}\text{F}]$fluoride PET/CT studies at our institution from 2009 to 2010. Fluoride uptake and calcification in major arteries, including coronary arteries, were analyzed by both visual assessment and standardized uptake value measurement.

Results: Fluoride uptake in vascular walls was demonstrated in 361 sites of 54 (96%) patients, whereas calcification was observed in 317 sites of 49 (88%) patients. Significant correlation between fluoride uptake and calcification was observed in most of the arterial walls, except in those of the abdominal aorta. Fluoride uptake in coronary arteries was demonstrated in 28 (46%) patients and coronary calcifications were observed in 34 (56%) patients. There was significant correlation between history of cardiovascular events and presence of fluoride uptake in coronary arteries. The coronary fluoride uptake value in patients with cardiovascular events was significantly higher than in patients without cardiovascular events.

Conclusion: sodium $[^{18}\text{F}]$fluoride PET/CT might be useful in the evaluation of the atherosclerotic process in major arteries, including coronary arteries. An increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk.

**Heart Disease**
Research published in January 2012\textsuperscript{41} concluded that there was a direct correlation between the fluoride level in arteries, including coronary arteries, and atherosclerosis, such that the scanning for the fluoride level could be used to diagnose the level of disease.

It found a direct relationship between the fluoride level and the patient’s history of heart disease, and concluded that “an increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk.”

This confirms many studies showing a relationship between fluoride and heart disease, as discussed in detail below.

Perhaps most importantly, this unquestionably proves that fluoride does accumulate in soft tissue – something fluoridation promoters deny emphatically, claiming it all goes to the bones or teeth, and never the soft tissues.


Ercan Varol \textit{et al}, \textit{Biological Trace Element Research}, Volume 133, Number 2 / February, 2010

This research shows fluoride affects the aorta (main artery) and heart in ways that lead to increased heart attacks.

This confirms findings from the earliest days of water fluoridation in the USA that deaths from heart attacks sky-rocketed in the fluoridated communities, compared with the non-fluoridated ones. This is shown by official US government data.

The heart beat rate slows, and heart rate abnormalities increase, in direct proportion to increasing fluoride levels. This occurred at the relatively low fluoride levels that cause symptoms mistaken for arthritis, in NZ as elsewhere according to WHO.

Elevated blood-fluoride levels lower available body calcium. Low calcium is directly related to impaired heart function. Extremely low calcium causes cardiac arrest. This is how acute lethal doses of fluoride (about 1-1/2 tablespoons) work – by starving the heart of calcium until it stops.

Research published in 2010 shows fluoride affects the aorta (main artery) and heart in ways that lead to increased heart attacks.\textsuperscript{42} (This refutes claims by fluoridation promoters that fluoride does not accumulate in soft tissue – it does, particularly arteries, ligaments, skeletal muscle, and the brain.)

\textsuperscript{41} Li, Yuxin; Berenji, Gholam R.; Shaba, Wisam F.; Tafti, Bashir; Yevdayev, Ella; Dadparvar, Simin — Association of vascular fluoride uptake with vascular calcification and coronary artery disease” \textit{Nuclear Medicine Communications}: January 2012, Volume 33, Issue 1; p 14–20

\textsuperscript{42} Ercan Varol \textit{et al}, \textit{Biological Trace Element Research} Feb 2010, \textit{Science of The Total Environment} May 2010
This confirms earlier studies showing high blood-fluoride levels have an effect on body calcium, leading to calcification of the aorta and other arteries.\textsuperscript{43,44}

Further research shows that the heart beat rate slows, and heart rate abnormalities increase, in direct proportion to increasing fluoride levels. This occurred at the relatively low fluoride levels that cause symptoms mistaken for arthritis, in NZ as elsewhere according to WHO. Fluoride accumulates over a period of 20 to 40 years to reach the -Class 1‖ level (that has this effect), shown in the chart below. Arsenic and fluoride (both high in the water supplies under study) were seen to be able to exert toxic effects independently. Fluoride’s effects were evident at water at levels of 0.2 mg/L or more of fluoride.\textsuperscript{45,46}

![Abnormal ECG Chart](image)

In laboratory studies, cultured myocardial cells of mice were adversely affected by fluoride.\textsuperscript{47} Statistically significant increases in the concentrations of sodium and potassium, and decreases in calcium and phosphorus concentrations were observed in rats given fluoride.\textsuperscript{48}

While many studies quoted here were conducted in areas with high fluoride levels in drinking water, total fluoride exposure today is at a similar level. Further, since fluoride is a cumulative poison, lower levels of fluoride will have a more subtle long-term effect, thus increasing heart problems – still the number one killer in our society.

This research confirms findings from the earliest days of water fluoridation in the USA that deaths from heart attacks sky-rocketed in the fluoridated communities, compared with the non-fluoridated ones:

\textsuperscript{43} Song et al —Observations on fluorotic aorta sclerosis by two-dimensional echo cardiography‖ Endemic diseases Bulletin 5, 1990, (1) 91-93

\textsuperscript{44} Liang et al —Investigation and analysis of cardiovascular disease in endemic and non-endemic fluorosis areas‖ He Bei Province Journal of Endemiology 12, (1984) 44.

\textsuperscript{45} Wang et al, —Toxicity From Water Containing Arsenic and Fluoride in Xinjiang‖ Fluoride Vol. 30 No. 2 81-84 1997


\textsuperscript{47} Qin CD et al —Effect of fluoride on spontaneous electrical activity of cultured myocardial cells‖ Chinese Journal of Endemiology 7, 1988, (5) 270-273

\textsuperscript{48} R. J. Verma and D. M. Gunsherlin —Hypocalcaemia in parental and F\textsubscript{1} generation rats treated with sodium fluoride—Food and Chemical Toxicology Volume 40, Issue 4, April 2002, Pages 551-554
Japanese researchers found that children with dental fluorosis have a higher incidence of heart damage than those without fluorosis. Chinese researchers showed an increase in abnormal heart rhythm in patients with dental fluorosis.

NZ studies show twice as many children in fluoridated areas have dental fluorosis than do non-fluoridated children. This epidemic of dental fluorosis in NZ shows that even our children are at risk of heart problems from fluoridation.

4 Increased Pre-term Birth Rates

(a) Research from India, 2010

The sample group was introduced to two interventions:
(1) removal of fluoride from ingestion through drinking water, food and other sources,
(2) counselling based intake of essential nutrients

Urine fluoride levels decreased in 53-67%
Haemoglobin levels increased upon withdrawal of fluoride followed by nutritional intervention in 73% - 83%

The percentage of pre-term deliveries decreased

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50 Wang et al, ―Toxicity From Water Containing Arsenic and Fluoride in Xinjiang" Fluoride Vol. 30 No. 2 81-84 1997
51 ―Effective interventional approach to control anaemia in pregnant women" A. K. Susheela1, N. K. Mondal1, Rashmi Gupta1, Kamla Ganesh1, Shashikant Brahmankar1, Shammi Bhasin2 and G. Gupta2 CURRENT SCIENCE, VOL. 98, NO. 10, 25 MAY 2010; 1320 - 1330

1Fluorosis Research and Rural Development Foundation, 34, I.P. Extension, Delhi 110 092, India
2Department of OBGY, Deen Dayal Upadhyay Hospital, Hari Nagar, New Delhi 110 064, India
Birth weight of babies enhanced in 77 - 80% in sample group as opposed to 47-49% in the control group. The number of low birth weight babies was reduced to 20% - 23%, as opposed to 51% - 53%.

**Researchers’ conclusion:**
Maternal and child under-nutrition and anaemia is not necessarily due to insufficient food intake but because of the derangement of nutrient absorption due to damage caused to GI, mucosa by *ingestion of undesirable chemical substance, viz. fluoride* through food, water and other sources.

These findings provide a new path for reducing the burden of disabled and mentally challenged children by reducing percentage of low birth weight babies [through reduction of fluoride intake during pregnancy].
The annual incidence of preterm birth (PTB) (<37 weeks gestation) in the United States is approximately 10%

Associated with considerable morbidity and mortality.

Based on current literature, theoretically one would expect water fluoridation to be protective against PTB. The opposite was found.

**Study results:**
- Risk of PTB 6.34% in women exposed to water fluoridation
- Risk of PTB 5.52% in women NOT exposed to water fluoridation
- Difference 15%

Relationship was most pronounced among women in the lowest SES groups (>10% poverty) and those of non-white racial origin.

Domestic water fluoridation was independently associated with an increased risk of PTB in logistic regression, after controlling for age, race/ethnicity, neighborhood poverty level, hypertension, and diabetes.

**US 1950 – 1969. 20 city study**

Infant mortality rate per 1000 live births for **non-whites:**
- Fell by 9.03 in the non-fluoridated cities.
- Fell by only 1.93 in the fluoridated cities
  - = 4.7 times better in non-fluoridated cities

Infant mortality rate per 1000 live births for **whites:**
- Fell by 5.22 in the non-fluoridated cities.
- Fell by only 3.33 in the fluoridated cities
  - = 1.7 times better in non-fluoridated cities

Reduction in improvement due to fluoridation in non-whites was 2.8 times more (i.e. worse) than in whites.

**Chile 1976**

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53 **Fluoride – the Aging Factor**, J Yiamouyiannis, Health Action Press 1986

54 Schatz A. Increased Death Rates in Chile with Artificial Fluoridation of Drinking Water, with Implications for other Countries. *Journal of Arts Humanities and Science* Vol 2 No1 January 1976 :1-17.
Research of Dr Albert Schatz, discoverer of streptomycin, the first cure for tuberculosis.
Data is from Chilean Government records.
Curico: 1ppm fluoride
San Fernando: 0% fluoride

<table>
<thead>
<tr>
<th>Cause of Death 1953-63</th>
<th>City (fluoride)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
<td>Curico</td>
<td>3.1 %</td>
</tr>
<tr>
<td>Extra deaths = 244%</td>
<td>San Fernando</td>
<td>0.9 %</td>
</tr>
<tr>
<td>Digestive system</td>
<td>Curico</td>
<td>18 per 10,000</td>
</tr>
<tr>
<td>Extra deaths = 50%</td>
<td>San Fernando</td>
<td>12 per 10,000</td>
</tr>
<tr>
<td>Total infant mortality</td>
<td>Curico</td>
<td>56.5 per 10,000</td>
</tr>
<tr>
<td>Extra deaths = 69%</td>
<td>San Fernando</td>
<td>33.4 per 10,000</td>
</tr>
<tr>
<td>All causes, all age groups</td>
<td>Curico</td>
<td>2255</td>
</tr>
<tr>
<td>Extra deaths = 16%</td>
<td>San Fernando</td>
<td>1003</td>
</tr>
</tbody>
</table>

(e) New Zealand Calculations

Total annual births 2011: 63180
Infant mortality rate: 6.7%
Neonatal deaths due to extreme preterm birth: 69.8 per 100,000 births (23.7%)
(Note: other fatal conditions can be caused by preterm birth, so the is a minimum impact calculation)
At 15% increase in preterm births (State University of New York study), extra deaths: 6.6 (if all NZ fluoridated)
Currently 55% NZ fluoridated
Current deaths due to fluoridation-induced extreme preterm births: 3.6
Maori/Pacific have 1.5 times the birth rate and 1.33 times the infant death rate as Europeans = twice as many deaths per woman
The 6.6 average is therefore distributed as 4.2 for Europeans and 2.4 for Maori/Polynesian
Maori/Polynesian deaths are 37% of the total, but they are only 22% of the population
The 3.6 average is distributed as 2.3 for Europeans and 1.3 for Maori/Polynesian
But preterm birth can lead to other problems as well. “Other perinatal conditions” caused 36.5% of neonatal deaths.
So the real death rate due to fluoridation is probably twice this much.
Source: The Children’s Social Health Monitor NZ; Census 2006
5  Osteosarcoma

(a) Summary
The best research to date is that published by Elise Bassin in 2006. This showed that boys, but not girls, who were exposed to fluoride such as through water fluoridation between the ages of six and eight inclusive are 500 to 700% more likely to contract osteosarcoma in their teens. Osteosarcoma invariably is fatal or requires limb amputation to save the victim’s life.

Between 3 and 4 young NZ men are affected by osteosarcoma each year. On the basis of Bassin’s research, at least two of those are due to fluoridation.

Accordingly, it is likely that fluoridating Councils in NZ are collectively responsible for killing two young men each year through their fluoridation programmes.

The study by Chester Douglass, that was promised as a “larger study that would disprove Bassin’s findings” was published in July 2011. Not only was it smaller than Bassin’s study – so small to be statistically unreliable – it did not even address Bassin’s finding of age-related risk, let alone disprove her finding. Publication of this study exonerates Bassin, and opens the door to class legal action against all those who fluoridate their water supplies.

(b) Detail

(i) Observations in 1955
There were observations on cortical bone defects observed in the Newburgh-Kingston study (1945-55) prompted Donald Taves to make the following comment in a report published by the National Academies of Science in 1970:

“There was an observation in the Kingston-Newburgh (Ast et al, 1956) study that was considered spurious and has never been followed up. There was a 13.5% incidence of cortical defects in bone in the fluoridated community but only 7.5% in the non-fluoridated community... Caffey (1955) noted that the age, sex, and anatomical distribution of these bone defects are `strikingly' similar to that of osteogenic sarcoma. While progression of cortical defects to malignancies has not been observed clinically, it would be important to have direct evidence that osteogenic sarcoma rates in males under 30 have not increased with fluoridation.” (our emphasis).

Osteogenic sarcoma, now called osteosarcoma, is a rare but frequently fatal bone cancer.

This observation by Caffey in 1955, and underlined by Taves in 1970, was the beginning of long history of the possibility that fluoridation may increase the incidence of osteosarcoma in young men. Before we get to that history, we will first look at the "biological plausibility" of a fluoride-osteosarcoma link, which is widely acknowledged in the scientific literature.

(ii) Biological plausibility
The 3 key findings supporting the plausibility of a fluoride/osteosarcoma connection are:

1) The bone is the principal site for fluoride accumulation within the body, and the rate of accumulation is increased during periods of bone development. Thus, the cells in the bone, particularly during the growth spurts, may be exposed to some of the highest fluoride concentrations in the body.

2) The preponderance of laboratory evidence indicates that fluoride can be mutagenic given sufficiently high concentrations (most mutagens are carcinogens) cause chromosome damage and interfere with the enzymes involved with DNA repair in a variety of cell and tissue studies (Tsutsui 1984; Caspary 1987; Kishi 1993 and Mihashi 1996). Recent studies have also found a correlation between fluoride exposure and chromosome damage in humans (Sheth 1994; Wu 1995; Meng 1997 and Joseph 2000).

3) Fluoride is a 'mitogen' - meaning it can stimulate the proliferation of bone-forming cells (osteoblasts). Osteosarcoma is a cancer caused by an abnormal proliferation of the osteoblasts.

Thus, fluoride's ability to induce mutagenic damage in fluoride-rich environments coupled with its ability to stimulate proliferation of osteoblasts provides a compelling biological basis by which fluoride could cause, or contribute to, osteosarcoma.

According to the authors of the NRC (2006) report:

"Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in non-dividing states." (NRC, 2006, p.275)

According to Bassin (2006):

"It is biologically plausible that fluoride affects the incidence rate of osteosarcoma, and that this effect would be strongest during periods of growth, particularly in males. First, approximately 99% of fluoride in the human body is contained in the skeleton with about 50% of the daily ingested fluoride being deposited directly into calcified tissue (bone or dentition). Second, fluoride acts as a mitogen, increasing the proliferation of osteoblasts and its uptake in bone increases during periods of rapid skeletal growth. In the young, the hydroxyapatite structure of bone mineral exists as many extremely small crystals each surrounded by an ion-rich hydration shell, providing a greater surface area for fluoride exchange to occur."

(iii) An historical overview of fluoride and osteosarcoma (1990 – 2009)

After the observations of Caffey (1955) and the recommendation based upon them by Donald Taves (NAS, 1970) that rates of osteosarcoma in males under 30 be investigated in fluoridated communities, it took another 20 years before this suggestion was followed. Meanwhile, in the 1970’s Dr. JohnYiamouyiannis, a biochemist, and Dr. Dean Burk, former head of the Cytochemistry Section of the National Cancer Institute, stirred up a hornet's nest when they published a study
claiming a greater increase in cancer rates after fluoridation was introduced into 10 US cities compared to 10 other US cities which were not fluoridated.

Robert Hoover and others at the National Cancer Institute attempted to rebut these findings and they were soon joined by several other epidemiologists including Kinlen and Sir Richard Doll in the UK who claimed to have looked at the same data and found no such relationship. However, the furore generated led to full scale Congressional hearings, which took place in 1977.

After listening to both sides in this debate, Congress ordered animal studies to determine whether fluoride causes cancer under laboratory conditions. The National Toxicology Program (NTP), under the U.S. Public Health service, commissioned Battelle Memorial labs to do these studies. Oral, liver and bone cancer received special attention. The results, which should have been completed and released in 1980, were not finally released until 1990.

II.D.5.b.iii.1 NTP animal study (1990)

Battelle found several cancers but they were all downgraded (see below) except osteosarcoma. The Battelle researchers found a dose-related increase in osteosarcoma in MALE (but not female) rats exposed to fluoride (Bucher et al., 1990; Bucher et al., 1991 and DHHS, 1991). After reviewers had removed one of the osteosarcomas, this finding was classified as "equivocal evidence of cancer."

Commenting on these NTP findings a committee from the World Health Organization (WHO) made the following comment:

"Such a (dose-dependent) trend associated with the occurrence of a rare tumour in the tissue in which fluoride is known to accumulate cannot be casually dismissed." (WHO, 2002)

Later, in 1996, Mihashi and Tsutsui lent further credibility to the NTP result, when they were able to demonstrate that fluoride caused chromosomal aberrations in a time and dose dependent manner in cultured cells derived from the vertebral bones of the same strain of rats (F344/N) used in the NTP rat study. Effects were observed at 4.3 ppm fluoride, a level which can be anticipated in key microenvironments in the bone in vivo. They argued that their results, "demonstrate that NaF is clastogenic to rat vertebral body-derived cells, providing a mechanistic basis for NaF to induce osteosarcomas in NaF-treated rats."

II.D.5.b.iii.2 Other cancers found in NTP study

The NTP study also reported an increase in liver and oral cancers, and an increase in the incidence of thyroid follicular cell tumors. However, a government-review panel downgraded all the non-bone cancers with a questionable rationale (Marcus 1990). One of the cancers downgraded was a rare form of liver cancer called hepatocholangiocarcinoma. The peer reviewers examining the slides claimed that this was not hepatocholangiocarcinoma but Dr. Melvin Reuber, an independent pathologist formerly with the National Cancer Institute, who was the first to describe this rare form of liver cancer, concurred with the pathologist at the Battelle Memorial Laboratory that this was indeed a case of hepatocholangiocarcinoma. In light of the importance of this study, the union representing professionals working at
the EPA headquarters in Washington, DC, has requested that Congress establish an independent review to re-examine these cancer slides (Hirzy 2000). Meanwhile, the NTP finally prompted the National Cancer Institute to review osteosarcoma rates in fluoridated communities in the US (which Taves had recommended 20 years earlier in 1990, see above).

II.D.5.b.iii.3 Department of Health and Human Services (DHHS)

The NTP study results were first made public in a report from the Department of Health and Human Services (DHHS) entitled Review of Fluoride: Benefits and Risks, published in February 1991. This same report also contained in Appendices E and F an analysis of the SEER registries by the Robert Hoover et al. from the National Cancer Institute (NCI) which we will discuss next.

II.D.5.b.iii.4 NCI Survey of the SEER registries for osteosarcoma (1991)

The National Cancer Institute (NCI) examined the nine SEER cancer registries (which cover about 10% of the US population) for bone cancer. The NCI found a greater increase in osteosarcoma in young males (but not for young females) in fluoridated versus non-fluoridated counties (Hoover et al, 1991 a)) However, the same authors, using a subset of the data claimed that they did not find that this increase was related to duration of exposure and discounted the original finding (Hoover et al., 1991 b). Today, more credibility is given to Hoover et al.’s first finding (Hoover et al., 1991 a) than their second (which supposedly discounted the first). This is largely because by the time the NCI authors had used a subset of the data and divided it between 4 different age ranges of exposure, there were so few cases left in each grouping that the study lacked any statistical power (Hoover et al., 1991 b). However, at the time their second finding certainly helped fluoridation promoters to downgrade concern on this issue.

Later, both Yiamouyiannis (1993) and Takahashi (2001) examined the same data base used by Hoover et al. and found a significant increase in osteosarcoma in young males in fluoridated counties.

(iv) McGuire et al., 1991

A small study published in the April 1991 issue of the Journal of the American Dental Association, warning that a finding of a relationship between fluoridation and osteosarcoma would threaten the water fluoridation program, reported that fluoride might actually be protective against osteosarcoma. One of the co-authors of this study was Professor Chester Douglass from the Harvard Medical School (see more below).

(v) Cohn, 1992

In 1992, Cohn, working for the NJ Health department, reported a significant increase in osteosarcoma in young males in the fluoridated communities in three NJ counties – but again not for young females (Cohn, 1992). Most significantly Cohn suggested that there might be a time frame where young boys are particularly vulnerable to fluoride’s carcinogenic effect. Cohn wrote:
If rapidly growing bone in adolescent males is most susceptible to the development of osteosarcomas (Glass and Fraumeni, 1970), it is possible that fluoride acts as a cancer promoter during a narrow window of susceptibility. The interplay of hormonal influences and the intensity of the growth spurts may be potent influences. Since fluoride is toxic to cells and a variety of enzymes at high concentrations (reviewed by Kaminsky et al., 1990; and Public Health Service, 1991), it may exert tumor promoting effects in the osteoblast cell microenvironment during bone deposition. Genetic predisposition may also play a role.” (Cohn, 1992, p.11.) (our emphasis)

(vi) Other studies

Other epidemiological studies of various sizes and quality have failed to find this relationship (Hrudy, 1990; Mahoney 1991; Freni, 1992; McGuire, 1991; Gelberg, 1995; Moss, 1995). For a full review of these studies and other studies on osteosarcoma see the submission to the National Research Council by the Fluoride Action Network (Connett, Neurath and Connett, 2005 a and b).

(vii) Elise Bassin, 2001

Elise Bassin is a dentist. She investigated a possible relationship between exposure to fluoride and osteosarcoma as part of her PhD thesis at the Harvard Dental School. Suspecting a possible time window of vulnerability for this problem (as Cohn had conjectured it might, see above) Bassin examined osteosarcoma rates as a function of which years the boys were exposed to fluoride.

In a matched case-control study, Bassin found, in what she herself described as a “robust finding,” that young boys exposed to fluoride in their 6th - 8th years (which corresponds to the mid-childhood growth spurt) had a 5 to 7 fold increased risk of succumbing to osteosarcoma by the age of 20. Her thesis was successfully defended in 2001 (Bassin, 2001).

II.D.5.b.vii.1 Bassin's PhD thesis hidden from the scientific community

It is extraordinary that after Bassin’s thesis was successfully defended in 2001, that it was neither followed up with a swift publication of her results nor any kind of statement made to warn the scientific community or the public about her findings. After all, if she was correct, a chemical being given daily to over 170 million Americans in their drinking water, might actually be killing people! If this discovery had been made by industrial researchers on an industrial chemical and the authors had hidden the findings from government regulators they would have been in serious trouble.

II.D.5.b.vii.2 Professor Chester Douglass

Professor Chester Douglass was Bassin’s thesis adviser and signed off on her thesis in 2001. Clearly, he knew what she had found and knew the serious implications of her findings. A paper on the same subject that Douglass had co-authored makes this abundantly clear (McGuire et al., 1991). However, even though he was given several opportunities to do so, Douglass neither warned his colleagues in professional meetings (e.g. a meeting organized by the British Fluoridation Society in 2002), nor
the NRC panel nor his funders at the NIH (NIEHS had put over $1 million financing Douglass’ work). Instead of warnings he did the very opposite. He continued to assert that ‘his’ work showed no significant association between fluoride and osteosarcoma. In his written comments to the NRC panel he even gave Bassin’s thesis as a footnote, but without indicating that her findings contradicted what he was telling the panel.

Finally, Michael Connett, of the Fluoride Action Network, acting on a tip off, went to the Harvard Medical School Rare Books Room in January 2005 and ‘discovered’ the ‘hidden’ thesis.

(viii) Bassin et al., 2006

Bassin’s findings were finally published in May 2006 (Bassin et al, 2006). However, the same issue of the journal published a letter from Chester Douglass, downplaying the significance of her findings. It is interesting to contrast Douglass’s ‘slowness’ to warn the public of Bassin’s findings in the four year period between 2001 and 2005, with the speed with which he warned the public that her findings might be ‘premature’ on the very same day that her article appeared in press.

Bassin\(^{55}\) demonstrated that boys, but not girls, exposed to fluoridated water between the ages of 6 and 10 have a 500-700% increased risk of developing osteosarcoma (a usually fatal form of bone cancer) in their teenage years. This confirmed an earlier study by the New Jersey Department of Health\(^{56}\) (1992)

No research has ever contradicted Bassin’s findings.

Approximately four to five NZ teenage males die each year from osteosarcoma. On the weight of evidence, it appears the majority could easily be due to fluoridation. The Ministry of Health is not concerned since they have not seen a cluster of these cancers. Firstly, it is difficult to see how five boys can form a cluster. Further, the fact that being exposed between ages 6 and 8 is the likely risk time and that diagnosis does not occur until late teens no one would expect to find a cluster unless they found out where these boys living when they were younger.

\(^{55}\) Age-specific fluoride exposure in drinking water and osteosarcoma (United States).

II.D.5.b.viii.1  The Douglass letter

In his letter Douglass claimed that Bassin's findings were based on a subset of a larger cohort, and that the larger cohort did not support her thesis (Douglass & Joshipura, 2006). This was strange because he provided no evidence that her methodology had, at that time, been applied to this larger cohort. Nor is it clear that it has ever been applied to the larger cohort. Douglass further claimed that his larger study (to be co-authored by Robert Hoover who was mentioned above in connection with the NCI review of the SEER cancer registries) would be published in the Summer of 2006.

Douglass had first mentioned the publication date of his study as being the Summer of 2006 in a personal communication to the NRC panel on Jan 3, 2006 (NRC, 2006, p. 329).

(ix)  Douglass study\textsuperscript{57}

Bassin found a 500\% to 600\% increased risk for young boys, exposed to fluoride in their 6th to 8th years, of later developing osteosarcoma. Douglass' study does not address exposure during this critical period because it measured the level of fluoride in bone, which accumulates fluoride over a lifetime. These bone levels provide no information about when the person was exposed to fluoride.

\textsuperscript{57} Chester Douglass et al "An Assessment of Bone Fluoride and Osteosarcoma," \textit{Journal of Dental Research} 28 July 2011
Not only does Douglass' study fail to refute Bassin's main finding, it suffers from other serious weaknesses:

1) Douglass' study was much smaller and weaker than Bassin's. It had only 20 control subjects under age 30, a fifth of Bassin's. For this key age group, Douglass' study was so small it could provide no reliable conclusions. Even Douglass admitted this serious limitation.

2) Douglass' choice of comparison group is suspect. Douglass compared the bone fluoride level of patients with osteosarcoma to "controls" with other forms of bone cancer. If fluoride also causes these other bone cancer types, then one would not expect to find any difference in bone fluoride between these groups. It is biologically plausible that fluoride could cause other bone cancers because it reaches such high concentrations in bone. One of the only studies of fluoride and non-osteosarcoma bone cancers did find a link, but this evidence was never mentioned by Douglass.

3) The controls were severely mismatched to the cases. Controls were much older (median 41 yrs) than the cases (18 yrs). The risk of osteosarcoma is highly age-dependent. Also, fluoride builds up in bone with age. Given Douglass' small sample size, it is unlikely he could have adequately compensated for the gross mismatch in age, especially because of these two simultaneous age dependencies. The groups were also mismatched on sex ratio, and osteosarcoma risk is well known to be sex dependent. Properly adjusting for sex and age would be virtually impossible.

In 2006 Elise Bassin's study was published in Cancer Causes and Control. It showed that boys, but not girls, when exposed to fluoride, such as in fluoridated drinking water, between the ages of 6 and 8, had over 5 times the risk of contracting osteosarcoma as teenagers. In a letter to the editor, Chester Douglass, Bassin's PhD supervisor and long-time fluoridation supporter, promised his larger study would disprove Bassin's study, even though he had signed it off and said it was —nice analysis. There's nothing wrong with that analysis."

In fact his study in much smaller than Bassin's. Even Douglass admitted the study was so small it could provide no reliable conclusions.

It also has very poor case control, unlike Bassin's which had excellent case control. Douglass' control group averaged 41 years old – against the osteosarcoma cases which were in their teens. There was also a significant gender imbalance, yet the effect is specific to males only.

(x) NZ Ministry of Health’s denial of Bassin’s work
The Ministry of Health and DHBs have falsely claimed that Bassin’s study had been discredited. The National Fluoridation Information Service has since repeated the claim - there are major methodological flaws in the two main studies”.

We asked NFIS what they were referencing, under the Official Information Act. NFIS confirmed it referred to Bassin and Sandhu.

Regarding Bassin, three sources were quoted, none of which is valid:
1. The Health Impact Assessment (HIA), prepared by three Hawke's Bay Medical Officers of Health in 2009. In criticising Bassin, the HIA relies on Douglass and Joshipura, discussed below.
2. The NHMRC Review 2007, which in fact gave Bassin's study a quality rating of "fair to good". It made some criticisms of methodology, as one would expect from a systematic review, but not to the extent claimed by the NFIS, and not all criticisms were valid. (For example it criticised the fact that the fluoridated individuals drank less bottled water. But if they drank (unfluoridated) bottled water, they would not have been in the "fluoridated" group, as Bassin estimated individual fluoride intake!).
3. The opinion of "Professor" Cox, director of NZ's cancer epidemiology group at Otago University medical faculty (which promotes fluoridation). In fact Mr Cox is an Associate Professor only; not a full professor. However, the NFIS has no correspondence from Mr Cox – it seems to be relying on the Hawke's Bay HIA document, which refers to a private communication from Mr Cox to an unspecified recipient. We asked Mr Cox for his analysis supporting the claim in his communication. He has never conducted an analysis of Bassin's study, hence his opinion has no validity. Neither could he recall any correspondence with the HIA authors.

The facts

Bassin’s study was conducted as PhD research. Her methodology was approved by her PhD supervisor, and Harvard University's doctoral board. Her thesis was later published in the journal *Cancer Causes and Control* in May 2006 (Bassin et al., 2006). Her thesis supervisor, and fluoridation promoter, in a letter to the same issue of this journal, (Douglass and Joshipura, 2006) claims that his larger work did not find the same relationship as Bassin.

Douglass' study was published in July 2011.
1. It was a smaller, not larger, study than Bassin’s.
2. It had major methodological flaws
3. It did not address age-related exposure at all – Bassin’s key finding.
4. It only measured bone fluoride levels, which relates to total lifetime exposure. This is known to be irrelevant.

We are aware of no *bona fide* criticism of her methodology, published in any internationally recognized peer-reviewed journal – the standard required by the Ministry of Health. Those who politically promote fluoridation inappropriately quote this letter to the editor – essentially a broken promise - as scientific proof that Bassin was wrong.
Another study examining osteosarcoma rates in New Jersey (New Jersey Department of Health [Cohn] 1992) also found a 5 – 7 fold increased risk of osteosarcoma in young males living in fluoridated areas of three counties compared to non-fluoridated areas. Other epidemiological studies have not found this association but Bassin’s study is the only one that pursued the possibility of the actual timing of fluoride exposure and this risk. The 6th, 7th and 8th years in which she found an increased risk corresponds to the mid-childhood growth spurt in which there is rapid bone turnover a situation which makes a tissue more vulnerable to genetic damage. Consequently other studies do not in any way refute Bassin’s study. It would be like looking in trees and concluding there are no earthworms in NZ – if you look in the wrong place you will never find what you are looking for.

Number of NZ cases
Health officials quote approximately 3.5 deaths from osteosarcoma of adolescent males per year in NZ. Around 55-60% of NZers drink fluoridated water, and those in unfluoridated communities get it in soft drinks, processed food, etc. If Bassin and Cohn are right, at least 2 of those deaths are caused by fluoridation. Is it acceptable to kill 2 young men each year because fluoridation might reduce tooth decay? Even when the main, and perhaps only, way fluoride strengthens enamel is by use of fluoride toothpaste or professional fluoride dental applications?

Blood fluoride study
The study on blood-fluoride levels was by Sandhu (2009). It was peer reviewed by experts before being published in an internationally recognised journal.

NFIS’ response to our information request
Regarding Sandhu, no published analysis or critique had been sighted, or was available to support the claim. The NFIS relied on the alleged “expertise” of the three Hawke’s Bay Medical Officers of Health who authored the HIA report. No evidence of such alleged expertise was provided. No scientific critique is included or referred to by them in the HIA report – they just express a view consistent with their contractual obligations to the Ministry of Health to support fluoridation policy.

6 Pineal Gland Accumulation
In 2001, Luke showed that fluoride accumulates in the pineal gland (up to 21,000 ppm). She had previously shown, in 1997, that such accumulation reduces melatonin production by the gland, resulting in earlier onset of puberty. For girls, this

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may increase the risk of breast cancer, as the risk is thought to be related to the time period between first menstruation and first pregnancy.

Earlier onset of menstruation in girls was also identified in fluoridated Newburgh compared with non-fluoridated Kingston (by 5 months) in the original 1945-1955 trial. 62

Melatonin is also involved in sleep cycles. Disrupted sleep causes reduced immunity to disease.

7 Bottle-fed Infants
There has been a series of recommendations in relation to “safe” levels of fluoride for children.

- SENES Oak Ridge Risk Assessment Center recommendation to EPA: **0.4 ppm** as an interim measure only until a (likely lower) safe level is scientifically determined (2010). (Note: Kumar’s data discussed in this report suggests 0.3 ppm would be safer)

- ANZFA (now FSANZ) report P93 on the infant formula standard, (1999). Water fluoridated at 0.7 ppm or more poses a risk to infants, either on its own or in infant formula.

- 3rd International Workshop on Fluorosis Prevention and Defluoridation of Drinking Water (in conjunction with WHO) recommended **at most 0.5 ppm** (2000)

- The US Public Health Services (CDC branch) of 0.7 ppm (2006)

- The American Dental Association of 0.7 ppm (2006, repeated 2009)

Research in Hong Kong (2006) shows that there remains measurable dental fluorosis at 0.5 ppm.

SCHER’s recommendation of 0.8 ppm is based on “moderate” dental fluorosis, which represents a significantly higher level of risk than mild, and is inappropriately high. This likely reflects the heavy weighting of pro-fluoridation panel members.

It should be noted that FSANZ did not scientifically review the issue of exposure of infants to fluoride in its 2006 decision on fluoridated packaged water.

FSANZ’ only review involving fluoride is in relation to allowing fluoridated packaged (bottled) water to be sold, and stated it was not reviewing toxicity as it addressed the issue on “equivalence” to fluoridated public drinking water. FSANZ did not address the US National Research Council Review’s analysis on infant exposure to fluoride.


This confirms (p 9) that the highest risk for fluorosis is from birth to 5 years for the permanent incisors, and from birth to 8 years for the other permanent teeth.

It also states that fluoride tablets should not be given to children aged 3 and under. Tablets are stated as being intended to be dissolved in water. They deliver the same daily dose as fluoridated water. As children in the 1990s typically drank water by the glass, rather than sipper bottles used today, it is difficult to see any material difference in consumption profiles, such as would lead to “spike” levels of fluoride. This indicates that fluoridated water should also not be given to children under 3 at all.

It identified that in the 1950s the target level of fluoride was 0.9 to 1.1 ppm. It recommended that in the 1990s, due to increased levels of ambient fluoride exposure, this should be in the range 0.7 to 1 ppm.

It also states that it is believed that increased dietary fluoride is not of concern. However, since no research on adverse health effects had or has ever been conducted, this belief appears to have no scientific foundation.

(i) SCHER’s recommendation
The reason for SCHER’s higher level is that it set “moderate” dental fluorosis as the threshold for concern. Medically, any level of dental fluorosis is a concern, as dental fluorosis is caused by fluoride poisoning of the cells that make the tooth enamel, and the teeth are the window to the bones. As SCHER noted, there is no lower threshold for fluoride accumulation in teeth or bone.

(ii) Comments on the Need for Revision of the NPDWT for Fluoride, K Theissen PhD, SENES Oak Ridge Inc., Center for Risk Analysis
This report, prepared for the US Environmental Protection Association, which commissioned the National Research Council review, recommends and interim level of 0.4 ppm while a true safe level is determined. This is likely to be lower than 0.4 ppm.

The report was prepared by Environmental Risk Assessment expert Dr Kathleen Theissen, who was appointed to the NRC panel specifically for this expertise. Dr Theissen had no views on fluoride before joining the NRC panel.

(iii) Levels of intake
The figures in the following table, derived from (pro-fluoridation) Kumar 2009, are reasonably consistent with NZ data. It suggests that 0.3 ppm may not present a significantly greater risk than "no" fluoride (typically <0.1 ppm in NZ).

On this basis, lowering Kapiti's fluoride level to 0.7 ppm would reduce dental fluorosis to 27%; lowering to 0.5 ppm would lower it to 21%; and reducing the level to 0.4 ppm would lower it to 18%.

<table>
<thead>
<tr>
<th>Water fluoride concentration (mg/L)</th>
<th>Children with caries (%)</th>
<th>Children with fluorosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.3</td>
<td>55.5</td>
<td>14.6</td>
</tr>
<tr>
<td>0.3-0.7</td>
<td>54.6</td>
<td>19.6</td>
</tr>
<tr>
<td>0.7-1.2</td>
<td>54.4</td>
<td>25.2</td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>56.4</td>
<td>40.5</td>
</tr>
</tbody>
</table>

\(^a\) Data for permanent teeth of children ages 7-17, calculated from data provided in Table 1 of Iida and Kumar (2009).

\(^b\) Includes very mild, mild, moderate, and severe fluorosis, but not "questionable."
According to the latest research in New Zealand, children in areas with fluoridated water at 0.7ppm will exceed the maximum stipulated daily intake 30% of the time, which is arguably too high as it is set at the level of moderate dental fluorosis, without considering other adverse health effect risks. At 1ppm the limit is exceeded 93% of the time. This is due to the fluoride in the water, not the formula powder.

Fluoridation promoters have tried to dismiss this as only a 30% risk of a child exceeding the maximum. This is like saying there is only a risk of getting lung cancer from smoking, so smoking is safe. The difference in terminology merely reflects a difference in focus, in a statistical analysis, between an individual and a whole population. A statistical 30% risk for an individual translates into a 30% incidence across a population.

Hong et al (see below) also established that fluoride intake needed to be less than 0.05 mg/kg per day for dental fluorosis not to occur.

The following intake levels are derived from Plunket data on consumption and manufacturers’ recommendations.

<table>
<thead>
<tr>
<th>Bottle/Breast fed</th>
<th>Age</th>
<th>Weight</th>
<th>Fluoride content per litre</th>
<th>Daily intake</th>
<th>Total Fluoride Intake</th>
<th>Mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle fed</td>
<td>Birth</td>
<td>3.5kg</td>
<td>0.8mg</td>
<td>600mls</td>
<td>0.48mg (0.6 x 0.8)</td>
<td>0.137mg/kg per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0024mg (0.6 x 0.004)</td>
<td>0.0006mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>6 mths</td>
<td>8kg</td>
<td>0.8mg</td>
<td>1 litre</td>
<td>0.8mg (1 x 0.8)</td>
<td>0.1mg/kg per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004mg</td>
<td>0.0005mg/kg per day</td>
</tr>
</tbody>
</table>

**Thyroid calculations**

The National Research Council —Fluoride in Drinking Water 2006” chapter 8, Effects on the Endocrine System, found that in humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate. Bottle fed babies are getting a dose that is associated with an effect on the thyroid, even when iodine intake is adequate.

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(v) **Children, and Infants under 6 months.**

*Hong et al 2006*\(^{64}\)

Hong et al showed that fluoridated water posed a risk up to the age of 4 years, with the risk being greatest in the first year of life, declining with each successive year.

This study used definitive Fluorosis Risk Index or severe fluorosis on both maxillary incisors as the required severity.

It found the first year was the most important in terms of risk, with successive years remaining significant, with progressively reducing importance.

Average fluoride intake was 0.040 to 0.057 mg/kg bwt/day, with higher levels in the first year.

**Current limits**

The limit of 1 ppm, set in the 1940s, was based on older children and adults.

It is acknowledged that toxicology for very young children (under 6) is likely to be quite different than for older children and adults. Consequently, the levels set on the basis of older children cannot be applied to children under 6 – there is simply no toxicological data to support safety of any specific fluoride level.

It is important to consider the following:

The “Adequate Intake” for infants under 6 months under the Australia- NZ nutrient reference values 2006 (p 176) is 0.01 mg/day. The maximum is 0.7 mg/day, without any scientific basis.

The level for 7 – 12 months, which we consider is not scientifically justified, is likely to be met from ambient exposure to fluoride, without consuming fluoridated water:

Supplements may be necessary for older infants in non-fluoridated areas. However, it is likely that many older infants and younger children are already ingesting 0.4-0.6 mg fluoride per day from foods, beverages and toothpaste alone (Burt 1992). A study of 60, 11–13 month old New Zealand infants (Chowdhury et al 1990) showed that total intake including fluoride from tablets and toothpastes ranged from 0.093 to 1.299 mg fluoride/day in fluoridated areas and from 0.039 to 0.720 mg fluoride/day in non-fluoridated areas. The fluoride from the diet (food and drink) ranged from 0.089 to 0.549 mg day in the fluoridated areas, and 0.038 to 0.314 mg day in the non-fluoridated areas.

Note: -AI” means “Adequate Intake”. This term is does not have its normal English meaning. It is a scientific term meaning that no scientifically verified requirement has been established, unlike vitamins and essential minerals (eg. daily requirements for Vitamin C or iodine). It is literally a guess, based on common exposure –with no apparent adverse effects” which, of course, are not researched in any fluoridated

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country, including NZ and Australia. Consequently, "Adequate Intake" has no scientific basis in NZ.

### RECOMMENDATIONS BY LIFE STAGE AND GENDER

<table>
<thead>
<tr>
<th>Infants</th>
<th>AI</th>
<th>Fluoride</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>0.01 mg/day</td>
<td></td>
</tr>
<tr>
<td>7–12 months</td>
<td>0.50 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

**Rationale:** The AI for 0–6 months was calculated by multiplying together the average intake of breast milk (0.78 L/day) and the average concentration of fluoride in breast milk of 0.013 mg/L (Dabelea et al 1996, FNB/IOM 1997) for mothers in areas with fluoridated water. Levels in formulas can vary widely depending on the concentration in the water used to reconstitute it. The AI for 0–6 months was based on extensive documentation about relationships between caries, water concentrations and fluoride intake (FNB/IOM 1997). A level of 0.05 mg/kg/day confers a high level of protection against caries and is not associated with unwanted health effects. Assuming a standard weight of 9 kg, this gives an AI of 0.5 mg/day. Infants living in non-fluoridated areas will not easily achieve the AI for fluoride, so supplements have been recommended based on life stage and level of water fluoridation.

**Special note:** Australian data have shown that prolonged consumption of infant formulas reconstituted with optimally-fluoridated water beyond 12 months of age could result in excessive amounts of fluoride being ingested during development of the enamel of the anterior permanent teeth and therefore may be a risk factor for fluorosis of these teeth (Silva & Reynolds 1996).

**Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders**

If fluoride is now classed as "an emerging neurotoxin" (*The Lancet*, 2007) in relation to the developing brain, the younger the infant the greater the risk. The key principles are discussed in this Scientific Consensus Statement. This is supported by Grandjean 2007.

In February 2008, a scientific consensus statement, developed by the Collaborative on Health and the Environment's Learning and Developmental Disabilities Initiative was issued, outlining the current understanding of links between environmental factors and developmental disabilities in children.

Fluoride was discussed as a substance of concern.

The statement concludes:

"Given the serious consequences of learning and developmental disabilities, a precautionary approach is warranted to protect the most vulnerable of our society."

"The central question, which is still unresolved, is what level of exposure results in harmful health effects to children. Children's small size means that, pound-for-pound of body weight, they receive a greater dose of fluoride than adults."

"The primary question remains as to whether exposures to fluoride via multiple routes of exposure, from drinking water, food and dental-care products, may result in a high enough cumulative exposure to contribute to developmental effects."

**Children at heightened risk**
"The development of the human brain begins in utero and continues through adolescence, following a precise and delicate step-by-step sequence involving complex neurobiological processes... The long and complex development of the brain and nervous system leaves it susceptible to the adverse effects of chemical exposures."

"For their body weight, children eat and breathe more than adults, thus a small exposure translates into a big dose."

"Children are often more susceptible than adults to the effects of exposure to environmental agents."

**Variations in individual susceptibility**

"Due to genetic variation people differ in susceptibility to exposures. Not identifying and studying susceptible subgroups can result in failure to protect those at high risk."

"As our testing methods have become more sophisticated, the recognition of individual sensitivity and, in particular, the sensitivity of the developing nervous system to the effects of environmental agents has grown."

(vi) **Letter re: 3rd International Workshop on Fluorosis Prevention and Defluoridation of Drinking Water**

The international Society for Dental fluorosis, working in conjunction with the World Health Organisation, concluded that at most the limit should be 0.5 ppm, and possibly lower.

Naturally-occurring fluoride in water is such a problem that commencing in 1995 international workshops on fluorosis prevention and defluoridation of water have been organized in collaboration with WHO.

In a letter written as an outcome of the November 2000 "3rd International Workshop on Fluorosis Prevention and Defluoridation of Water", the participants agreed that their shared consensus should be presented to WHO as a basis to seriously reconsider certain parts of the "WHO draft publication WSH/DRAFT/99.9 Fluoride in Drinking Water" before its mass publication.

On Chapter 5 "Guidelines and Standards". The figure "1.5" mg/L being associated with the WHO guideline, of which its advocacy is "a level at which dental fluorosis should be minimal", has been puzzling us for over the past ten years. Why is it "1.5"?; what scientific data is the figure based on? Theoretically as well as empirically, the figure seems to be far above the proven safety level. There is already ample evidence that the so-called recommendation level of 1.5 mg/L could cause dental fluorosis for an entire community in a number of developing countries. Additionally, if this chapter is read in conjunction with Chapter 3 "Human Health Risks", its meanings are immediately nullified.

There was "a high degree of consensus" among attendees at the 3rd International Workshop on Fluorosis Prevention and Defluoridation of Water that:
i) WHO's Guidelines and Standards of 1.5 parts per million fluoride for water supplies "is far above the proven safety level."

iv) All other factors being equal, the recommended figure of "1.5" should be reduced as far down as "0.5" which is the figure that many of us ethically found to be the maximum tolerable range.

Wong et al 2006

Even at 0.5 ppm fluoride, 32.4% of 12 year olds had enamel defects.

The rate at 0.85 ppm would have been 74.2%, compared with 32-33% in NZ. The relationship was linear.

In NZ the rate of fluorosis in unfluoridated communities (typically around 0.1ppm) is 15-16%.

If we apply a linear calculation, confirmed as appropriate by the 2008 Auckland study (referencing Ellwood and Fejerskov 2003), we find that lowering the level of fluoride to 0.7ppm would only reduce fluorosis rates to around 29%.

Reducing fluoride to 0.5ppm would reduce fluorosis to around 24%, and reducing fluoride to 0.4 ppm would reduce fluorosis rates to around 22%.

The relationship between enamel defects and fluoride consumption has been well established for over 70 years [Churchill, 1931; Dean, 1934]. The prevalence of developmental defects of enamel (DDE) increases with increasing concentration of fluoride in the drinking water [Clarkson and O'Mullane, 1989; Milsom and Mitropoulos, 1990; Ellwood and O'Mullane, 1995; Angelillo et al., 1999; Ekanayake and van der Hoek, 2003]. However, the chosen concentration of fluoride to be added to the water supply has frequently been determined empirically without regard for dietary or other sources of fluoride [Evans et al., 1987; Moola, 1996]. Therefore, the prevalence of enamel defects should be monitored carefully to achieve and maintain the efficacy and safety of water fluoridation. That is, the optimum concentration of fluoride in a communal water supply should be the amount that provides maximum caries reduction and a clinically insignificant level of enamel defects.

Wong H, McGrath C, Lo E, King N — Association between Developmental Defects of Enamel and Different Concentrations of Fluoride in the Public water supply" Caries Research 2006; 40; 481-486
Abstract

Objectives: To compare the prevalence and severity of developmental defects of enamel (DDE) among subjects whose maxillary incisors developed during periods with different concentrations of fluoride in the public water supply. Methods: Standardized intra-oral photographs of random samples of 12-year-old children were collected in 1983, 1991 and 2001 (n = 1,990) in Hong Kong and assessed for DDE by a trained masked examiner. The fluoride concentrations in the public water supply at the times when the enamel on their maxillary incisors developed were 1.0, 0.7 and 0.5 ppm, respectively. Results: The mouth prevalence of DDE for these children (based on the maxillary incisors) were 92.1, 55.8 and 35.2% in the years 1983, 1991 and 2001, respectively (p < 0.001). Most of these children were affected by diffuse opacities (89.3% in 1983, 48.5% in 1991 and 32.4% in 2001, p < 0.001). Marked differences in the mean number of teeth affected by DDE (p < 0.001) and in the maximum extent of DDE (p < 0.002) between 1983, 1991 and 2001 were also observed. Conclusions: A decrease in the preva-

Discussion

There are limitations to the use of a single photograph of maxillary incisors when assessing DDE [Wong et al., 2005]. However, when data from this photographic study of the 1983 sample are compared with those from a clinical study of the same sample [King, 1990], there appears to be no difference because the mouth prevalence figure of DDE on the maxillary incisors reported by King [1990] in a clinical assessment was 91.9% (F = 1.0 ppm) compared with 92.1% (F = 1.0 ppm) found in this study. The comparability of these figures gives testimony to the use of photographs as an alternative to clinical examination when a standardized approach is employed.

8 Arthritis

WHO recognised the dangers of even low doses of fluoride taken over many years. In its 1970 publication Fluorides and Human Health it stated:

"At higher levels of ingestion - from 2 to 8 mg daily, skeletal fluorosis may arise

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... Whereas dental fluorosis is easily recognised, the skeletal involvement is not clinically obvious until the advanced stage of crippling fluorosis... early cases may be misdiagnosed as rheumatoid or osteoarthritis."

1993 - Polish pediatricians found abnormal bone changes in 11 to 15 year-olds exhibiting dental fluorosis. 67

2000 - A British Medical Journal study reports that older white women from fluoridated communities have a 32% higher rate of wrist fracture. 68

2001 - A Mexican study also links dental fluorosis to increased bone fractures. 69

2001 - A Rheumatology International study links naturally fluoridated water to knee osteoarthritis in amounts many Americans consume daily. 70

2006 - Wrist x-rays reveal that 96% of Tibetan children with dental fluorosis had "developmental skeletal abnormalities" including carpal bone hardening or thickening. 71

(i) Bone accumulation of fluoride and skeletal fluorosis

The following selection of studies show the accumulation of fluoride in bone (measured as bone ash) at a range of water-fluoride levels. Note that one study found fluoride levels equivalent to Stage I skeletal fluorosis with less than 0.5ppm fluoride in the drinking water:


Place: Grand Rapids, Michigan, USA
Water F Content: 1 ppm (11 years)
No. of Samples: 5
F-Bone Concentrations (Mean): 2,250 ppm (iliac crest); 2,410 ppm (rib); 3,230

69 M Teresa Allarcon-Herrera et al, "Wellwater Fluoride Dental Fluorosis And Bone Fractures In the Guadiana Valley of Mexico" Fluoride 2001 Vol.34 No.2 139-149
71 Jin Cao, Yan Zhao, Yi Li, Hui Jun Deng, Juan Yi and Jian Wei Liu, "Fluoride levels in various black tea commodities: Measurement and safety evaluation," Food and Chemical Toxicology Volume 44, Issue 7, July 2006, Pages 1131-1137
ppm (vertebra).
F-Bone Concentrations (Maximum): 4,022 ppm (vertebra)


Place: Leeds, England
Water F Content: <0.5 ppm
No. of Samples: 42
F-Bone Concentration (Mean): 3,211 ppm (trabecular bone, rib)
F-Bone Concentration (Maximum): 6,660 ppm (trabecular bone, rib)

Place: The South Shields, England
Water F Content: 0.8 - 1.2 ppm
No. of Samples: 27
F-Bone Concentration (Mean): 4,141 ppm (trabecular bone, rib)
F-Bone Concentration (Maximum): 4,563 ppm (trabecular bone, rib)

Table 1

<table>
<thead>
<tr>
<th>OSTEOSCLEROTIC PHASE</th>
<th>ASH CONCENTRATION (mgF/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Bone</td>
<td>500 - 1,000</td>
</tr>
<tr>
<td>Preclinical Phase (asymptomatic; slight radiographically-detectable increases in bone mass)</td>
<td>3,500 - 5,500</td>
</tr>
<tr>
<td>Clinical Phase I (sporadic pain; stiffness of joints; osteosclerosis of pelvis and vertebral column)</td>
<td>6,000 - 7,000</td>
</tr>
<tr>
<td>Clinical Phase II (chronic joint pain; arthritic symptoms; slight calcification of ligaments' increased osteosclerosis/cancellous bones; with/without osteoporosis of long bones)</td>
<td>7,500 - 9,000</td>
</tr>
<tr>
<td>Phase III: Crippling Fluorosis (limitation of joint movement; calcification of ligaments/neck, vert. column; crippling deformities/spine &amp; major joints; muscle wasting; neruological defects/compression of spinal cord)</td>
<td>8,400</td>
</tr>
</tbody>
</table>

Earlier in the 20th century, fluoride was prescribed by a number of European doctors to reduce the activity of the thyroid gland for those suffering from hyperthyroidism (over active thyroid) (Merck Index, 1960, p. 952; Waldbott, et al., 1978, p. 163). With water fluoridation, we are forcing people to drink a thyroid-depressing medication which could serve to promote higher levels of hypothyroidism (underactive thyroid) in the population, and all the subsequent problems related to this disorder. Such problems include depression, fatigue, weight gain, muscle and joint pains, increased cholesterol levels, and heart disease.

It bears noting that according to the Department of Health and Human Services (1991) fluoride exposure in fluoridated communities is estimated to range from 1.58 to 6.6 mg/day, which is a range that actually overlaps the dose (2.3 - 4.5 mg/day) shown to decrease the functioning of the human thyroid (Galletti & Joyet, 1958).

The Effects Of Fluoride On The Thyroid Gland

By Dr Barry Durrant-Peatfield MBBS LRCP MRCS
Medical Advisor to Thyroid UK

Dr Barry Durrant-Peatfield obtained his Medical degrees in 1960 at Guy's Hospital London. He left the NHS in 1980 to specialise in thyroid illnesses drawing inspiration from the work of infamous Dr Broda Barnes, at the Foundation that bears his name, Connecticut, USA. He has been a medical practitioner for over forty years specialising in metabolic disorders during which time he became a leading authority in the UK for thyroid and adrenal management. For over twenty years he also ran a successful private clinic and became a nation-wide leading authority on thyroid and adrenal dysfunction, but clashed with establishment medicine in the management of thyroid illness. He is the author of The Great Thyroid Scandal (see opposite page), he currently lectures at nutritional colleges in London as well as conducting his own teaching seminars. Barry will shortly be opening a diagnostic clinic in the UK for thyroid and adrenal disorders where he will provide advice on diagnosis and treatment with special interests in nutritional aspects.

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Web site: http://www.drpeatfield.com
There is a daunting amount of research studies showing that the widely acclaimed benefits on fluoride dental health are more imagined than real. My main concern however, is the effect of sustained fluoride intake on general health. Again, there is a huge body of research literature on this subject, freely available and in the public domain.

But this body of work was not considered by the York Review when their remit was changed from "Studies of the effects of fluoride on health" to "Studies on the effects of fluoridated water on health." It is clearly evident that it was not considered by the BMA (British Medical Association), British Dental Association (BDA), BFS (British Fluoridation Society) and FPHM, (Faculty for Public Health and Medicine) since they all insist, as in the briefing paper to Members of Parliament - that fluoridation is safe and non-injurious to health.

This is a public disgrace, I will now show by reviewing the damaging effects of fluoridation, with special reference to thyroid illness.

It has been known since the latter part of the 19th century that certain communities, notably in Argentina, India and Turkey were chronically ill, with premature ageing, arthritis, mental retardation, and infertility; and high levels of natural fluorides in the water were responsible. Not only was it clear that the fluoride was having a general effect on the health of the community, but in the early 1920s Goldemberg, working in Argentina showed that fluoride was displacing iodine; thus compounding the damage and rendering the community also hypothyroid from iodine deficiency.

(i) Highly damaging to the thyroid gland

This was the basis of the research in the 1930s of May, Litzka, Gorlitzer von Mundy, who used fluoride preparations to treat over-active thyroid illness. Their patients either drank fluoridated water, swallowed fluoride pills or were bathed in fluoridated bath water; and their thyroid function was as a result, greatly depressed. The use in 1937 of fluorotyrosine for this purpose showed how effective this treatment was; but the effectiveness was difficult to predict and many patients suffered total thyroid loss. So it was given a new role and received a new name, Pardinon. It was marketed not for over-active thyroid disease but as a pesticide. (Note the manufacturer of fluorotyrosine was IG Farben who also made sarin, a gas used in World War II).

This bit of history illustrates the fact that fluorides are dangerous in general and in particular highly damaging to the thyroid gland, a matter to which I shall return shortly. While it is unlikely that it will be disputed that fluorides are toxic - let us be reminded that they are Schedule 2 Poisons under the Poisons Act 1972, the matter in dispute is the level of toxicity attributable to given amounts;
in today's context the degree of damage caused by given concentrations in the water supply. While admitting its toxicity, proponents rely on the fact that it is diluted and therefore, it is claimed, unlikely to have deleterious effects.

They could not be more mistaken

It seems to me that we must be aware of how fluoride does its damage. It is an enzyme poison. Enzymes are complex protein compounds that vastly speed up biological chemical reactions while themselves remaining unchanged. As we speak, there occurs in all of us a vast multitude of these reactions to maintain life and produce the energy to sustain it. The chains of amino acids that make up these complex proteins are linked by simple compounds called amides; and it is with these that fluorine molecules react, splitting and distorting them, thus damaging the enzymes and their activity. Let it be said at once, this effect can occur at extraordinary low concentrations; even lower than the one part per million which is the dilution proposed for fluoridation in our water supply.

Moreover, fluorides are cumulative and build up steadily with ingestion of fluoride from all sources, which include not just water but the air we breathe and the food we eat. The use of fluoride toothpaste in dental hygiene and the coating of teeth are further sources of substantial levels of fluoride intake. The body can only eliminate half of the total intake, which means that the older you are the more fluoride will have accumulated in your body. Inevitably this means the ageing population is particularly targeted. And even worse for the very young there is a major element of risk in baby formula made with fluoridated water. The extreme sensitivity of the very young to fluoride toxicity makes this unacceptable. Since there are so many sources of fluoride in our everyday living, it will prove impossible to maintain an average level of 1ppm as is suggested.

What is the result of these toxic effects?

First the immune system. The distortion of protein structure causes the immune proteins to fail to recognise body proteins, and so instigate an attack on them, which is Autoimmune Disease. Autoimmune diseases constitute a body of disease processes troubling many thousands of people: Rheumatoid Arthritis, Systemic Lupus Erythematosis, Asthma and Systemic Sclerosis are examples; but in my particular context today, thyroid antibodies will be produced which will cause Thyroiditis resulting in the common hypothyroid disease, Hashimoto's Disease and the hyperthyroidism of Graves' Disease.

Musculo-skeletal damage results further from the enzyme toxic effect; the collagen tissue of which muscles, tendons, ligaments and bones are made, is damaged. Rheumatoid illness, osteoporosis and deformation of bones inevitably follow. This toxic effect extends to the ameloblasts making tooth
enamel, which is consequently weakened and then made brittle; and its visible appearance is, of course, dental fluorosis.

The enzyme poison effect extends to our genes; DNA cannot repair itself, and chromosomes are damaged. Work at the University of Missouri showed genital damage, targeting ovaries and testes. Also affected is inter uterine growth and development of the foetus, especially the nervous system. Increased incidence of Down's Syndrome has been documented. Fluorides are mutagenic. That is, they can cause the uncontrolled proliferation of cells we call cancer. This applies to cancer anywhere in the body; but bones are particularly picked out. The incidence of osteosarcoma in a study reporting in 1991 showed an unbelievable 50% increase. A report in 1955 in the New England Journal of Medicine showed a 400% increase in cancer of the thyroid in San Francisco during the period their water was fluoridated.

My particular concern is the effect of fluorides on the thyroid gland

Perhaps I may remind you about thyroid disease. The thyroid gland produces hormones which control our metabolism - the rate at which we burn our fuel. Deficiency is relatively common, much more than is generally accepted by many medical authorities: a figure of 1:4 or 1:3 by mid life is more likely. The illness is insidious in its onset and progression. People become tired, cold, overweight, depressed, constipated; they suffer arthritis, hair loss, infertility, atherosclerosis and chronic illness. Sadly, it is poorly diagnosed and poorly managed by very many doctors in this country. What concerns me so deeply is that in concentrations as low as 1ppm, fluorides damage the thyroid system on 4 levels.

1. The enzyme manufacture of thyroid hormones within the thyroid gland itself. The process by which iodine is attached to the amino acid tyrosine and converted to the two significant thyroid hormones, thyroxine (T4) and liothyronine (T3), is slowed.

2. The stimulation of certain G proteins from the toxic effect of fluoride (whose function is to govern uptake of substances into each of the cells of the body), has the effect of switching off the uptake into the cell of the active thyroid hormone.

3. The thyroid control mechanism is compromised. The thyroid stimulating hormone output from the pituitary gland is inhibited by fluoride, thus reducing thyroid output of thyroid hormones.

4. Fluoride competes for the receptor sites on the thyroid gland which respond to the thyroid stimulating hormone; so that less of this hormone reaches the thyroid gland and so less thyroid hormone is manufactured.
These damaging effects, all of which occur with small concentrations of fluoride, have obvious and easily identifiable effects on thyroid status. The running down of thyroid hormone means a slow slide into hypothyroidism. Already the incidence of hypothyroidism is increasing as a result of other environmental toxins and pollutions together with widespread nutritional deficiencies.

(ii) Displaces iodine in the body

These figures would be worrying enough, since they mean that iodine deficiency, which results in hypothyroidism (thyroid hormone cannot be manufactured without iodine) is likely to affect huge numbers of people. What makes it infinitely worse, is that fluorine, being a halogen (chemically related to iodine), but very much more active, displaces iodine. So that the uptake of iodine is compromised by the ejection, as it were, of the iodine by fluorine. To condemn the entire population, already having marginal levels of iodine, to inevitable progressive failure of their thyroid system by fluoridating the water, borders on criminal lunacy.

References:

G Litzka - "Die experimentellen Grundlagen der Behandlung des Morbus Basedow und der Hyperthyreose mittels Fluortyrosin" Med Wochenschr 63:1037-1040 (1937) (discusses the basis of the use of fluorides in anti-thyroid medication, documents activity on liver, inhibition of glycolysis, etc.).


Sarin: (GB: isopropyl methylphosono-fluoride) is a colorless, odorless volatile liquid, soluble in water, first synthesized at IG Farben in 1938. It kills mainly through inhalation.

Cyclosarin (GF) and Thiosarin are variants. Pennsylvania Department of Health
http://www.dsf.health.state.pa.us/health/cwp/view.asp?a=171&q=233740
Laboratory investigations have often used aluminofluoride complexes for stimulation of various guanine nucleotide binding proteins. These complexes form spontaneously in aqueous solutions containing fluoride and traces of aluminum and appear to act as phosphate analogs. In view of the ubiquity of phosphate in cell metabolism and together with the dramatic increase in the amount of reactive aluminum now found in ecosystems, aluminofluoride complexes represent a strong potential danger for living organisms including humans. Although the possibility of pathophysiological consequences of their long-term action are not yet fully recognized, the pharmacological and toxicological effects of aluminofluoride complexes on animal and human cells, tissues, and organs are identified and summarized in this review.

Aluminofluoride complexes (AlFx) form spontaneously in aqueous solutions containing fluoride and traces of aluminum ions and appear to act as phosphate analogs. These complexes have become widely utilized in laboratory investigations of various guanine nucleotide-binding proteins. Reflecting on many laboratory studies, a new mechanism of fluoride and aluminum action on the cellular level is being suggested. The long-term synergistic effects of these ions in living environment and their hidden danger for human health are not yet fully recognized.

Aluminofluoride complexes appear to be a new class of phosphate analogs for laboratory investigations. Experimental data clearly indicate that aluminofluoride complexes stimulate various G proteins. These metallofluoride complexes may thus mimic or potentiate the action of numerous extracellular signals and significantly affect many cellular responses. The principle of amplification of the initial signal during its conversion into the functional response has been a widely accepted tenet in cell physiology. Fluoride ions in the presence of trace amounts of aluminum may therefore act with powerful pharmacological effects.

E SOCIAL IMPACTS OF FLUORIDATION
Attachments

*Scientific Knowledge in Controversy – the Social Dynamics of the Fluoridation Debate*, Martin B 1991

Scientific Knowledge in Controversy – synopsis by M Atkin.

Michael Easley document – Fluoridation Opponents

1  **Dental fluorosis**

According to Australian research, even relatively mild dental fluorosis, which is caused only by subclinical fluoride intoxication during tooth formation, has the same social-behavioural impact on children as overbite and crooked teeth, through self-consciousness and embarrassment.

According to the two most recent NZ studies, half of dental fluorosis is caused by water fluoridation directly. The “halo” effect of fluoridation likely contributes to some of the remaining incidence. The use of high strength fluoride toothpaste in children appears to also be a significant factor in the remaining 50% of cases.

2  **Social Dynamics of the Fluoridation debate**

This topic is covered in a masterful way in *Scientific Knowledge in Controversy – the Social Dynamics of the Fluoridation Debate*, Martin B 1991, attached to this paper, along with a synopsis.

3  **Personal attacks**

One of the hallmarks of this debate is the use of personal attacks, ridicule, denigration, and defamation by promoters against opponents. In NZ this tactic continues to this day. And it is institutionalised at the government level. Conversely, national groups opposing fluoridation typically conduct themselves with professionalism, and rely on science to make their case, eschewing personal attacks as a tactic. That is not to say there are not individuals opposed to fluoridation that take a more extreme approach. The attached document by Michael Easley, one of the most extreme denigrators of opponents, but essentially used by Government officials in NZ, is an example of the language of denigration used in the debate. Many of the tactics quoted are in fact used by fluoridation promoters, and the analysis of 250 “references” could equally apply to lists presented by promoters. Just as Mr Easley uses the term “health terrorists”, Dr Martin Lee of the Canterbury DHB, and long time fluoridation promoter for the Ministry of Health, has referred to opponents as “George Speights, with the mindset of Al Quaeda”.

Some examples in the NZ context are:

- In the 1950s all opponents of fluoridation were investigated for association with the communist party. None was found.
- In Kapiti in 2010, Dr Neal Stephen defamed Dr Kevin Baker, who spoke against fluoridation, claiming he did not have the qualifications from Cambridge University that he claimed. Reference to the published Medical Register proved the allegation false.
- Dr Stephen Palmer consistently lodges personal attacks against the two main opponents in the Hutt Valley. This has negatively impacted on his credibility with councillors.
- Dr Palmer has also focused on a list of tactics he attributes to opponents, yet he himself, and the NFIS, regularly use these tactics (attached)

The ongoing use of such tactics can only result in the diminution of trust and respect the public, and local authority councillors, hold for such officials.

**Public reaction**

Implementation of fluoridation in Hastings in 1954 led to the immediate establishment of the Hastings Anti-fluoridation Society. In establishing the Commission of Inquiry in 1955 the Government expected to end opposition to fluoridation. Instead, the Hastings group became a national body opposing fluoridation.

The “personal crusade” of Mayor Percy Dowse in Lower Hutt, no doubt pushed by Cr, later Mayor, dentist John Kennedy-Good, led to the officials of the Hutt Valley Ratepayers’ Association taking the Council to court. This led to the famous Privy Council case, for which individuals mortgaged their homes, such was their commitment to stop fluoridation.

As the Government began implementing fluoridation following the Privy Council decision, local opposition sprang up. For example, in both Timaru and Dunedin, the local councils implemented fluoridation against the votes of residents. In Timaru, Imelda Hitchcock led a 13 year campaign and ended fluoridation in 1985. In Dunedin, a small group led a similar campaign, unsuccessfully.

Currently there are a number of national groups opposing fluoridation.

- Fluoride Action Network NZ
- Weston A Price Foundation
- NZ Academy of Oral Medicine and Toxicology
- NZ Soil and Health Association
- NZ Health Trust
- Fluoridegate Legal Action NZ

**Abuse of institutional power**
Perhaps the most significant, yet unseen, social impact of fluoridation has been, not from fluoridation itself, but from the pursuit of fluoridation policy - the systematic (ab)use of institutional power by those promoting fluoridation policy to threaten, intimidate, coerce, and suppress opposition. The use of institutional power to attack and suppress individuals and research is brilliantly documented in the sociological research of Dr Brian Martin, published as —*Scientific Knowledge in Controversy – the Social Dynamics of the Fluoridation Debate*” 1991. The entire text is attached, along with a synopsis.

The manipulation of public health research in NZ, including a case study on fluoridation, is discussed in *Barriers to Public Health Research*, Farger *et al*, May 2001, Department of Public Health, Wellington Clinical School.

In relation to the Hastings experiment, the authors write:74

—*This case does give the impression of an influential group exerting professional and scientific power in order to influence public opinion and policy. This exercise of power involved suppression, manipulation and distortion of data in order to protect the [policy] of fluoridation.*”

and more generally:75

—*The fluoridation debate thus provides a good case study of the suppression of scientific knowledge by a profession through the suppression of scientific dissent.*”

Regarding the deliberate destruction of opponents’ careers by those promoting fluoridation, as discussed in Dr Martin’s research, some specific examples are:

- Dr Hardy Limeback, Head of Preventive Dentistry, University of Toronto: fired and reinstated with damages after suing the University
- Dr William Hirzy, President, EPA Union of Scientists: fired and reinstated with damages after suing the EPA
- Dr Phyllis Mullinex, Forsythe Dental School: fired, laboratory destroyed, career destroyed, when she published research showing fluoride neurotoxicity in laboratory rats: settled out of court.
- Dr Elise Bassin, published research showing a link between fluoridation and osteosarcoma in males: career attacked, will no longer speak about her research.

In NZ:

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74 *Barriers to Public Health Research*, Farger *et al*, May 2001, Department of Public Health, Wellington Clinical School p23
75 Ibid, p22.
• Dr John Colquhoun, Chief Dental Officer Auckland: published official figure showing high incidence of dental fluorosis in Auckland, which the Ministry had tried to suppress: career destroyed, death threats made against him and his family (confirmed by personal friend of Colquhoun, Dr Lawrie Brett, who received the same threats), forced into early retirement, still defamed to this day (13 years after his death).

• Dr Lawrie Brett BDS, was refused his degree by Otago University because he wrote the facts about fluoridation in write his thesis – he was told if he wanted his degree he would have to stay another year and a thesis that supported fluoridation. (Dr Brett had previously studied chemistry, and was aware that what the dental school was teaching about fluoride's alleged safety was incorrect).

• A New Plymouth dentist (name withheld) was told that if he spoke against fluoridation at the 2011 Tribunal hearings he could "forget about advancing a career in public health”

• Kevin Hague (now Green MP) while CEO of the West Coast District Health Board rewrote the DHB employment policy with the sole purpose of removing elected DHB member Mr David Tranter from the Board for speaking against fluoridation in his private capacity. The Board rejected the new policy outright as illegal. (This is of course on official record).

A perhaps unseen sociological impact is that as the population steadily learns more about the issue, and thereby come to oppose fluoridation (as confirmed by 2000 research in Onehunga by the Auckland Area Health Board\textsuperscript{76}), they become increasingly aware of politicians and health officials defending the practice with claims they know to be untrue. The public thereby concludes that those they should be able to trust are in fact untrustworthy, whether through ignorance or deliberate deceit. The likely long-term effect is inherent distrust of these individuals, even when they are promoting worthwhile public health policies.

\textsuperscript{76} L Holbrook and P Watson Fluoridation –What the Public Know and What They Want” (June 2001) \textit{The Australian and New Zealand Journal of Public Health}, 2001 vol 25 No. 4, 346.
Fluoride in Drinking Water: A Scientific Review of EPA's Standards

Committee on Fluoride in Drinking Water, National Research Council

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\textsuperscript{1}This study was planned, overseen, and supported by the Board on Environmental Studies and Toxicology.
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Preface

In 1986, the U.S. Environmental Protection Agency (EPA) established a maximum-contaminant-level goal (MCLG) of 4 milligrams per liter (mg/L) and a secondary maximum contaminant level (SMCL) of 2 mg/L for fluoride in drinking water. These exposure values are not recommendations for the artificial fluoridation of drinking water, but are guidelines for areas in the United States that are contaminated or have high concentrations of naturally occurring fluoride. The goal of the MCLG is to establish an exposure guideline to prevent adverse health effects in the general population, and the goal of the SMCL is to reduce the occurrence of adverse cosmetic consequences from exposure to fluoride. Both the MCLG and the SMCL are nonenforceable guidelines.

The regulatory standard for drinking water is the maximum contaminant level (MCL), which is set as close to the MCLG as possible, with the use of the best technology available. For fluoride, the MCL is the same as the MCLG of 4 mg/L. In 1993, a previous committee of the National Research Council (NRC) reviewed the health effects of ingested fluoride and EPA's MCL. It concluded that the MCL was an appropriate interim standard, but that further research was needed to fill data gaps on total exposures to fluoride and its toxicity. Because new research on fluoride is now available and because the Safe Drinking Water Act requires periodic reassessment of regulations for drinking water contaminants, EPA requested that the NRC evaluate the adequacy of its MCLG and SMCL for fluoride to protect public health. In response to EPA's request, the NRC convened the Committee on Fluoride in Drinking Water, which prepared this report. The committee was charged to review toxicologic, epidemiologic, and clinical data on fluoride,
particularly data published since 1993, and exposure data on orally ingested fluoride from drinking water and other sources. Biographical information on the committee members is provided in Appendix A.

This report presents the committee’s review of the scientific basis of EPA’s MCLG and SMCL for fluoride, and their adequacy for protecting children and others from adverse health effects. The committee considers the relative contribution of various sources of fluoride (e.g., drinking water, food, dental hygiene products) to total exposure, and identifies data gaps and makes recommendations for future research relevant to setting the MCLG and SMCL for fluoride. Addressing questions of economics, risk-benefit assessment, or water-treatment technology was not part of the committee’s charge.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC’s Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Kenneth Cantor, National Cancer Institute; Caswell Evans, Jr., University of Illinois at Chicago; Michael Gallo, University of Medicine and Dentistry of New Jersey; Mari Golub, California Environmental Protection Agency; Philippe Grandjean, University of Southern Denmark; David Hoel, Medical University of South Carolina; James Lamb, The Weinberg Group Inc.; Betty Olson, University of California at Irvine; Elizabeth Platz, Johns Hopkins Bloomberg School of Public Health; George Stookey, Indiana University School of Dentistry; Charles Turner, University of Indiana; Robert Utiger, Harvard Institute of Medicine; Gary Whitford, Medical College of Georgia; and Gerald Wogan, Massachusetts Institute of Technology.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by John C. Bailar, University of Chicago, and Gilbert S. Omenn, University of Michigan Medical School. Appointed by the NRC, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the individuals who made presentations to the committee at its public meetings. They include Paul Con
PREFACE

nett, St. Lawrence University; Joyce Donohue, EPA; Steve Levy, University of Iowa; William Maas, Centers for Disease Control and Prevention; Edward Ohanian, EPA; Charles Turner, Indiana University; and Gary Whitford, University of Georgia. The committee also wishes to thank Thomas Burke, Johns Hopkins University; Michael Morris, University of Michigan; Bernard Wagner, Wagner and Associates; and Lauren Zeise, California Environmental Protection Agency, who served as consultants to the committee.

The committee is grateful for the assistance of the NRC staff in preparing the report. It particularly wishes to acknowledge the outstanding staff support from project director Susan Martel. We are grateful for her persistence and patience in keeping us focused and moving ahead on the task and her expertise and skill in reconciling the differing viewpoints of committee members. Other staff members who contributed to this effort are James Reisa, director of the Board on Environmental Studies and Toxicology; Kulbir Bakshi, program director for the Committee on Toxicology; Cay Butler, editor; Mirsada Karalic-Loncarevic, research associate; Jennifer Saunders, research associate; and Tamara Dawson, senior project assistant.

Finally, I would like to thank all the members of the committee for their efforts throughout the development of this report.

John Doull, M.D., Ph.D., Chair
Committee on Fluoride in Drinking Water
Fluoride in Drinking Water: A Scientific Review of EPA’s Standards
http://www.nap.edu/catalog/11571.html
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Under the Safe Drinking Water Act, the U.S. Environmental Protection Agency (EPA) is required to establish exposure standards for contaminants in public drinking-water systems that might cause any adverse effects on human health. These standards include the maximum contaminant level goal (MCLG), the maximum contaminant level (MCL), and the secondary maximum contaminant level (SMCL). The MCLG is a health goal set at a concentration at which no adverse health effects are expected to occur and the margins of safety are judged “adequate.” The MCL is the enforceable standard that is set as close to the MCLG as possible, taking into consideration other factors, such as treatment technology and costs. For some contaminants, EPA also establishes an SMCL, which is a guideline for managing drinking water for aesthetic, cosmetic, or technical effects.

Fluoride is one of the drinking-water contaminants regulated by EPA. In 1986, EPA established an MCLG and MCL for fluoride at a concentration of 4 milligrams per liter (mg/L) and an SMCL of 2 mg/L. These guidelines are restrictions on the total amount of fluoride allowed in drinking water. Because fluoride is well known for its use in the prevention of dental caries, it is important to make the distinction here that EPA's drinking-water guidelines are not recommendations about adding fluoride to drinking water to protect the public from dental caries. Guidelines for that purpose (0.7 to 1.2 mg/L) were established by the U.S. Public Health Service more than 40 years ago. Instead, EPA's guidelines are maximum allowable concentrations in drinking water intended to prevent toxic or other adverse effects that could result from exposure to fluoride.

In the early 1990s at the request of EPA, the National Research Council...
FLUORIDE IN DRINKING WATER

(NRC) independently reviewed the health effects of ingested fluoride and the scientific basis for EPA's MCL. It concluded that the MCL was an appropriate interim standard but that further research was needed to fill data gaps on total exposure to fluoride and its toxicity. Because new research on fluoride is now available and because the Safe Drinking Water Act requires periodic reassessment of regulations for drinking-water contaminants, EPA requested that the NRC again evaluate the adequacy of its MCLG and SMCL for fluoride to protect public health.

COMMITTEE’S TASK

In response to EPA's request, the NRC convened the Committee on Fluoride in Drinking Water, which prepared this report. The committee was charged to review toxicologic, epidemiologic, and clinical data on fluoride—particularly data published since the NRC’s previous (1993) report—and exposure data on orally ingested fluoride from drinking water and other sources. On the basis of its review, the committee was asked to evaluate independently the scientific basis of EPA’s MCLG of 4 mg/L and SMCL of 2 mg/L in drinking water and the adequacy of those guidelines to protect children and others from adverse health effects. The committee was asked to consider the relative contribution of various fluoride sources (e.g., drinking water, food, dental-hygiene products) to total exposure. The committee was also asked to identify data gaps and to make recommendations for future research relevant to setting the MCLG and SMCL for fluoride. Addressing questions of artificial fluoridation, economics, risk-benefit assessment, and water-treatment technology was not part of the committee’s charge.

THE COMMITTEE’S EVALUATION

To accomplish its task, the committee reviewed a large body of research on fluoride, focusing primarily on studies generated since the early 1990s, including information on exposure; pharmacokinetics; adverse effects on various organ systems; and genotoxic and carcinogenic potential. The collective evidence from in vitro assays, animal research, human studies, and mechanistic information was used to assess whether multiple lines of evidence indicate human health risks. The committee only considered adverse effects that might result from exposure to fluoride; it did not evaluate health risk from lack of exposure to fluoride or fluoride’s efficacy in preventing dental caries.

After reviewing the collective evidence, including studies conducted since the early 1990s, the committee concluded unanimously that the present MCLG of 4 mg/L for fluoride should be lowered. Exposure at the MCLG clearly puts children at risk of developing severe enamel fluorosis,
Enamel hypoplasia is a condition that is associated with enamel loss and pitting. In addition, the majority of the committee concluded that the MCLG is not likely to be protective against bone fractures. The basis for these conclusions is expanded upon below.

**Exposure to Fluoride**

The major sources of exposure to fluoride are drinking water, food, dental products, and pesticides. The biggest contributor to exposure for most people in the United States is drinking water. Estimates from 1992 indicate that approximately 1.4 million people in the United States had drinking water with natural fluoride concentrations of 2.0-3.9 mg/L, and just over 200,000 people had concentrations equal to or exceeding 4 mg/L (the presented MCL). In 2000, it was estimated that approximately 162 million people had artificially fluoridated water (0.7-1.2 mg/L).

Food sources contain various concentrations of fluoride and are the second largest contributor to exposure. Beverages contribute most to estimated fluoride intake, even when excluding contributions from local tap water. The greatest source of nondietary fluoride is dental products, primarily toothpastes. The public is also exposed to fluoride from background air and from certain pesticide residues. Other sources include certain pharmaceuticals and consumer products.

Highly exposed subpopulations include individuals who have high concentrations of fluoride in drinking water, who drink unusually large volumes of water, or who are exposed to other important sources of fluoride. Some subpopulations consume much greater quantities of water than the 2 L per day that EPA assumes for adults, including outdoor workers, athletes, and people with certain medical conditions, such as diabetes insipidus. On a per-body-weight basis, infants and young children have approximately three to four times greater exposure than do adults. Dental-care products are also a special consideration for children, because many tend to use more toothpaste than is advised, their swallowing control is not as well developed as that of adults, and many children under the care of a dentist undergo fluoride treatments.

Overall, the committee found that the contribution to total fluoride exposure from fluoride in drinking water in the average person, depending on age, is 57% to 90% at 2 mg/L and 72% to 94% at 4 mg/L. For high-water-intake individuals, the drinking-water contribution is 86% to 96% at 2 mg/L and 92% to 98% at 4 mg/L. Among individuals with an average water-intake rate, infants and children have the greatest total exposure to fluoride, ranging from 0.079 to 0.258 mg/kg/day at 4 mg/L and 0.046 to 0.144 mg/kg/day at 2 mg/L in drinking water. For high-water-intake individuals exposed to fluoride at 4 mg/L, total exposure ranges from 0.294 mg/kg/day.
mg/kg/day for adults to 0.634 mg/kg/day for children. The corresponding intake range at 2 mg/L is 0.154 to 0.334 mg/kg/day for adults and children, respectively.

Dental Effects

Enamel fluorosis is a dose-related mottling of enamel that can range from mild discoloration of the tooth surface to severe staining and pitting. The condition is permanent after it develops in children during tooth formation, a period ranging from birth until about the age of 8. Whether to consider enamel fluorosis, particularly the moderate to severe forms, to be an adverse health effect or a cosmetic effect has been the subject of debate for decades. In previous assessments, all forms of enamel fluorosis, including the severest form, have been judged to be aesthetically displeasing but not adverse to health. This view has been based largely on the absence of direct evidence that severe enamel fluorosis results in tooth loss; loss of tooth function; or psychological, behavioral, or social problems.

Severe enamel fluorosis is characterized by dark yellow to brown staining and discrete and confluent pitting, which constitutes enamel loss. The committee finds the rationale for considering severe enamel fluorosis only a cosmetic effect to be much weaker for discrete and confluent pitting than for staining. One of the functions of tooth enamel is to protect the dentin and, ultimately, the pulp from decay and infection. Severe enamel fluorosis compromises that health-protective function by causing structural damage to the tooth. The damage to teeth caused by severe enamel fluorosis is a toxic effect that is consistent with prevailing risk assessment definitions of adverse health effects. This view is supported by the clinical practice of filling enamel pits in patients with severe enamel fluorosis and restoring the affected teeth. Moreover, the plausible hypothesis concerning elevated frequency of caries in persons with severe enamel fluorosis has been accepted by some authorities, and the available evidence is mixed but generally supportive.

Severe enamel fluorosis occurs at an appreciable frequency, approximately 10% on average, among children in U.S. communities with water fluoride concentrations at or near the current MCLG of 4 mg/L. Thus, the MCLG is not adequately protective against this condition.

Two of the 12 members of the committee did not agree that severe enamel fluorosis should now be considered an adverse health effect. They agreed that it is an adverse dental effect but found that no new evidence has emerged to suggest a link between severe enamel fluorosis, as experienced in the United States, and a person’s ability to function. They judged that demonstration of enamel defects alone from fluorosis is not sufficient to change the prevailing opinion that severe enamel fluorosis is an adverse cosmetic effect. Despite their disagreement on characterization of the condition, these
two members concurred with the committee’s conclusion that the MCLG should prevent the occurrence of this unwanted condition.

Enamel fluorosis is also of concern from an aesthetic standpoint because it discolors or results in staining of teeth. No data indicate that staining alone affects tooth function or susceptibility to caries, but a few studies have shown that tooth mottling affects aesthetic perception of facial attractiveness. It is difficult to draw conclusions from these studies, largely because perception of the condition and facial attractiveness are subjective and culturally influenced. The committee finds that it is reasonable to assume that some individuals will find moderate enamel fluorosis on front teeth to be detrimental to their appearance and that it could affect their overall sense of well-being. However, the available data are not adequate to categorize moderate enamel fluorosis as an adverse health effect on the basis of structural or psychological effects.

Since 1993, there have been no new studies of enamel fluorosis in U.S. communities with fluoride at 2 mg/L in drinking water. Earlier studies indicated that the prevalence of moderate enamel fluorosis at that concentration could be as high as 15%. Because enamel fluorosis has different distribution patterns among teeth, depending on when exposure occurred during tooth development and on enamel thickness, and because current indexes for categorizing enamel fluorosis do not differentiate between mottling of anterior and posterior teeth, the committee was not able to determine what percentage of moderate cases might be of cosmetic concern.

Musculoskeletal Effects

Concerns about fluoride’s effects on the musculoskeletal system historically have been and continue to be focused on skeletal fluorosis and bone fracture. Fluoride is readily incorporated into the crystalline structure of bone and will accumulate over time. Since the previous 1993 NRC review of fluoride, two pharmacokinetic models were developed to predict bone concentrations from chronic exposure to fluoride. Predictions based on these models were used in the committee’s assessments below.

Skeletal Fluorosis

Skeletal fluorosis is a bone and joint condition associated with prolonged exposure to high concentrations of fluoride. Fluoride increases bone density and appears to exacerbate the growth of osteophytes present in the bone and joints, resulting in joint stiffness and pain. The condition is categorized into one of four stages: a preclinical stage and three clinical stages that increase in severity. The most severe stage (clinical stage III) historically has been referred to as the “crippling” stage. At stage II, mobility is not significantly
affected, but it is characterized by chronic joint pain, arthritic symptoms, slight calcification of ligaments, and osteosclerosis of the cancellous bones. Whether EPA's MCLG of 4 mg/L protects against these precursors to more serious mobility problems is unclear.

Few clinical cases of skeletal fluorosis in healthy U.S. populations have been reported in recent decades, and the committee did not find any recent studies to evaluate the prevalence of the condition in populations exposed to fluoride at the MCLG. Thus, to answer the question of whether EPA's MCLG protects the general public from stage II and stage III skeletal fluorosis, the committee compared pharmacokinetic model predictions of bone fluoride concentrations and historical data on iliac-crest bone fluoride concentrations associated with the different stages of skeletal fluorosis. The models estimated that bone fluoride concentrations resulting from lifetime exposure to fluoride in drinking water at 2 mg/L (4,000 to 5,000 mg/kg ash) or 4 mg/L (10,000 to 12,000 mg/kg ash) fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis (4,300 to 9,200 mg/kg ash and 4,200 to 12,700 mg/kg ash, respectively). However, this comparison alone is insufficient for determining whether stage II or III skeletal fluorosis is a risk for populations exposed to fluoride at 4 mg/L, because bone fluoride concentrations and the levels at which skeletal fluorosis occurs vary widely. On the basis of the existing epidemiologic literature, stage III skeletal fluorosis appears to be a rare condition in the United States; furthermore, the committee could not determine whether stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L. Thus, more research is needed to clarify the relationship between fluoride ingestion, fluoride concentrations in bone, and stage of skeletal fluorosis before any conclusions can be drawn.

Bone Fractures

Several epidemiologic studies of fluoride and bone fractures have been published since the 1993 NRC review. The committee focused its review on observational studies of populations exposed to drinking water containing fluoride at 2 to 4 mg/L or greater and on clinical trials of fluoride (20-34 mg/day) as a treatment for osteoporosis. Several strong observational studies indicated an increased risk of bone fracture in populations exposed to fluoride at 4 mg/L, and the results of other studies were qualitatively consistent with that finding. The one study using serum fluoride concentrations found no appreciable relationship to fractures. Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to show an association might have been diminished in that study. A meta-analysis of randomized clinical trials reported an elevated risk of new nonvertebral fractures and a slightly decreased risk of vertebral
fractures after 4 years of fluoride treatment. An increased risk of bone fracture was found among a subset of the trials that the committee found most informative for assessing long-term exposure. Although the duration and concentrations of exposure to fluoride differed between the observational studies and the clinical trials, bone fluoride content was similar (6,200 to more than 11,000 mg/kg ash in observational studies and 5,400 to 12,000 mg/kg ash in clinical trials).

Fracture risk and bone strength have been studied in animal models. The weight of evidence indicates that, although fluoride might increase bone volume, there is less strength per unit volume. Studies of rats indicate that bone strength begins to decline when fluoride in bone ash reaches 6,000 to 7,000 mg/kg. However, more research is needed to address uncertainties associated with extrapolating data on bone strength and fractures from animals to humans. Important species differences in fluoride uptake, bone remodeling, and growth must be considered. Biochemical and physiological data indicate a biologically plausible mechanism by which fluoride could weaken bone. In this case, the physiological effect of fluoride on bone quality and risk of fracture observed in animal studies is consistent with the human evidence.

Overall, there was consensus among the committee that there is scientific evidence that under certain conditions fluoride can weaken bone and increase the risk of fractures. The majority of the committee concluded that lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure to 1 mg/L, particularly in some demographic subgroups that are prone to accumulate fluoride into their bones (e.g., people with renal disease). However, 3 of the 12 members judged that the evidence only supports a conclusion that the MCLG might not be protective against bone fracture. Those members judged that more evidence is needed to conclude that bone fractures occur at an appreciable frequency in human populations exposed to fluoride at 4 mg/L and that the MCLG is not likely to be protective.

There were few studies to assess fracture risk in populations exposed to fluoride at 2 mg/L in drinking water. The best available study, from Finland, suggested an increased rate of hip fracture in populations exposed to fluoride at concentrations above 1.5 mg/L. However, this study alone is not sufficient to judge fracture risk for people exposed to fluoride at 2 mg/L. Thus, no conclusions could be drawn about fracture risk or safety at 2 mg/L.

Reproductive and Developmental Effects

A large number of reproductive and developmental studies in animals have been conducted and published since the 1993 NRC report, and the
overall quality of that database has improved significantly. Those studies indicated that adverse reproductive and developmental outcomes occur only at very high concentrations that are unlikely to be encountered by U.S. populations. A few human studies suggested that high concentrations of fluoride exposure might be associated with alterations in reproductive hormones, effects on fertility, and developmental outcomes, but design limitations make those studies insufficient for risk evaluation.

Neurotoxicity and Neurobehavioral Effects

Animal and human studies of fluoride have been published reporting adverse cognitive and behavioral effects. A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence.

A few animal studies have reported alterations in the behavior of rodents after treatment with fluoride, but the committee did not find the changes to be substantial in magnitude. More compelling were studies on molecular, cellular, and anatomical changes in the nervous system found after fluoride exposure, suggesting that functional changes could occur. These changes might be subtle or seen only under certain physiological or environmental conditions. More research is needed to clarify the effect of fluoride on brain chemistry and function.

Endocrine Effects

The chief endocrine effects of fluoride exposures in experimental animals and in humans include decreased thyroid function, increased calcitonin activity, increased parathyroid hormone activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity. Some of these effects are associated with fluoride intake that is achievable at fluoride concentrations in drinking water of 4 mg/L or less, especially for young children or for individuals with high water intake. Many of the effects could be considered subclinical effects, meaning that they are not adverse health effects. However, recent work on borderline hormonal imbalances and endocrine-disrupting chemicals indicated that adverse health effects, or increased risks for developing adverse effects, might be associated with seemingly mild imbalances or perturbations in hormone concentrations. Further research is needed to explore these possibilities.
Effects on Other Organ Systems

The committee also considered effects on the gastrointestinal system, kidneys, liver, and immune system. There were no human studies on drinking water containing fluoride at 4 mg/L in which gastrointestinal, renal, hepatic, or immune effects were carefully documented. Case reports and in vitro and animal studies indicated that exposure to fluoride at concentrations greater than 4 mg/L can be irritating to the gastrointestinal system, affect renal tissues and function, and alter hepatic and immunologic parameters. Such effects are unlikely to be a risk for the average individual exposed to fluoride at 4 mg/L in drinking water. However, a potentially susceptible subpopulation comprises individuals with renal impairments who retain more fluoride than healthy people do.

Genotoxicity and Carcinogenicity

Many assays have been performed to assess the genotoxicity of fluoride. Since the 1993 NRC review, the most significant additions to the database are in vivo assays in human populations and, to a lesser extent, in vitro assays with human cell lines and in vivo experiments with rodents. The results of the in vivo human studies are mixed. The results of in vitro tests are also conflicting and do not contribute significantly to the interpretation of the existing database. Evidence on the cytogenetic effects of fluoride at environmental concentrations is contradictory.

Whether fluoride might be associated with bone cancer has been a subject of debate. Bone is the most plausible site for cancer associated with fluoride because of its deposition into bone and its mitogenic effects on bone cells in culture. In a 1990 cancer bioassay, the overall incidence of osteosarcoma in male rats exposed to different amounts of fluoride in drinking water showed a positive dose-response trend. In a 1992 study, no increase in osteosarcoma was reported in male rats, but most of the committee judged the study to have insufficient power to counter the evidence for the trend found in the 1990 bioassay.

Several epidemiologic investigations of the relation between fluoride and cancer have been performed since the 1993 evaluation, including both individual-based and ecologic studies. Several studies had significant methodological limitations that made it difficult to draw conclusions. Overall, the results are mixed, with some studies reporting a positive association and others no association.

On the basis of the committee’s collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro), the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and
mixed. Assessing whether fluoride constitutes a risk factor for osteosarcoma is complicated by the rarity of the disease and the difficulty of characterizing biologic dose because of the ubiquity of population exposure to fluoride and the difficulty of acquiring bone samples in nonaffected individuals.

A relatively large hospital-based case-control study of osteosarcoma and fluoride exposure is under way at the Harvard School of Dental Medicine and is expected to be published in 2006. That study will be an important addition to the fluoride database, because it will have exposure information on residence histories, water consumption, and assays of bone and toenails. The results of that study should help to identify what future research will be most useful in elucidating fluoride’s carcinogenic potential.

**DRINKING-WATER STANDARDS**

**Maximum-Contaminant-Level Goal**

In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that EPA’s MCLG of 4 mg/L should be lowered. Lowering the MCLG will prevent children from developing severe enamel fluorosis and will reduce the lifetime accumulation of fluoride into bone that the majority of the committee concludes is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis, which are particular concerns for subpopulations that are prone to accumulating fluoride in their bones.

To develop an MCLG that is protective against severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures, EPA should update the risk assessment of fluoride to include new data on health risks and better estimates of total exposure (relative source contribution) for individuals. EPA should use current approaches for quantifying risk, considering susceptible subpopulations, and characterizing uncertainties and variability.

**Secondary Maximum Contaminant Level**

The prevalence of severe enamel fluorosis is very low (near zero) at fluoride concentrations below 2 mg/L. From a cosmetic standpoint, the SMCL does not completely prevent the occurrence of moderate enamel fluorosis. EPA has indicated that the SMCL was intended to reduce the severity and occurrence of the condition to 15% or less of the exposed population. The available data indicate that fewer than 15% of children will experience moderate enamel fluorosis of aesthetic concern (discoloration of the front teeth) at that concentration. However, the degree to which moderate enamel fluorosis might go beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is not known.
SUMMARY

OTHER PUBLIC HEALTH ISSUES

The committee’s conclusions regarding the potential for adverse effects from fluoride at 2 to 4 mg/L in drinking water do not address the lower exposures commonly experienced by most U.S. citizens. Fluoridation is widely practiced in the United States to protect against the development of dental caries; fluoride is added to public water supplies at 0.7 to 1.2 mg/L. The charge to the committee did not include an examination of the benefits and risks that might occur at these lower concentrations of fluoride in drinking water.

RESEARCH NEEDS

As noted above, gaps in the information on fluoride prevented the committee from making some judgments about the safety or the risks of fluoride at concentrations of 2 to 4 mg/L. The following research will be useful for filling those gaps and guiding revisions to the MCLG and SMCL for fluoride.

• Exposure assessment
  — Improved assessment of exposure to fluoride from all sources is needed for a variety of populations (e.g., different socioeconomic conditions). To the extent possible, exposures should be characterized for individuals rather than communities, and epidemiologic studies should group individuals by exposure level rather than by source of exposure, location of residence, or fluoride concentration in drinking water. Intakes or exposures should be characterized with and without normalization for body weight. Fluoride should be included in nationwide biomonitoring surveys and nutritional studies; in particular, analysis of fluoride in blood and urine samples taken in these surveys would be valuable.

• Pharmacokinetic studies
  — The concentrations of fluoride in human bone as a function of exposure concentration, exposure duration, age, sex, and health status should be studied. Such studies would be greatly aided by noninvasive means of measuring bone fluoride. Information is particularly needed on fluoride plasma and bone concentrations in people with small-to-moderate changes in renal function as well as in those with serious renal deficiency.
  — Improved and readily available pharmacokinetic models should be developed. Additional cross-species pharmacokinetic comparisons would help to validate such models.

• Studies of enamel fluorosis
  — Additional studies, including longitudinal studies, should be done in U.S. communities with water fluoride concentrations greater than 1 mg/L.
These studies should focus on moderate and severe enamel fluorosis in relation to caries and in relation to psychological, behavioral, and social effects among affected children, their parents, and affected children after they become adults.

— Methods should be developed and validated to objectively assess enamel fluorosis. Consideration should be given to distinguishing between staining or mottling of the anterior teeth and of the posterior teeth so that aesthetic consequences can be more easily assessed.

— More research is needed on the relation between fluoride exposure and dentin fluorosis and delayed tooth eruption patterns.

• Bone studies
  — A systematic study of clinical stage II and stage III skeletal fluorosis should be conducted to clarify the relationship between fluoride ingestion, fluoride concentration in bone, and clinical symptoms.
  — More studies of communities with drinking water containing fluoride at 2 mg/L or more are needed to assess potential bone fracture risk at these higher concentrations. Quantitative measures of fracture, such as radiologic assessment of vertebral body collapse, should be used instead of self-reported fractures or hospital records. Moreover, if possible, bone fluoride concentrations should be measured in long-term residents.

• Other health effects
  — Carefully conducted studies of exposure to fluoride and emerging health parameters of interest (e.g., endocrine effects and brain function) should be performed in populations in the United States exposed to various concentrations of fluoride. It is important that exposures be appropriately documented.
Introduction

Under the Safe Drinking Water Act, the U.S. Environmental Protection Agency (EPA) is required to establish the concentrations of contaminants that are permitted in public drinking-water systems. A public water system is defined by EPA as a “system for the provision to the public of water for human consumption through pipes or other constructed conveyances, if such system has at least fifteen service connections or regularly serves at least twenty-five individuals” (63 Fed. Reg. 41940 [1998]). Section 1412 of the act, as amended in 1986, requires EPA to publish maximum-contaminant-level goals (MCLGs) and promulgate national primary drinking-water regulations (maximum contaminant levels [MCLs]) for contaminants in drinking water that might cause any adverse effect on human health and that are known or expected to occur in public water systems. MCLGs are health goals set at concentrations at which no known or expected adverse health effects occur and the margins of safety are adequate. MCLGs are not regulatory requirements but are used by EPA as a basis for establishing MCLs. MCLs are enforceable standards to be set as close as possible to the MCLG with use of the best technology available. For some contaminants, EPA also establishes secondary maximum contaminant levels (SMCLs), which are nonenforceable guidelines for managing drinking water for aesthetic, cosmetic, or technical effects related to public acceptance of drinking water.

Fluoride is one of the natural contaminants found in public drinking water supplies regulated by EPA. In 1986, an MCLG of 4 milligrams per liter (mg/L) and an SMCL of 2 mg/L were established for fluoride, and an MCL of 4 mg/L was promulgated. It is important to make the distinction that EPA's standards are guidelines for restricting the amount of naturally
occurring fluoride in drinking water; they are not recommendations about the practice of adding fluoride to public drinking-water systems (see below). In this report, the National Research Council’s (NRC’s) Committee on Fluoride in Drinking Water reviews the nature of the human health risks from fluoride, estimates exposures to the general public from drinking water and other sources, and provides an assessment of the adequacy of the MCLG for protecting public health from adverse health effects from fluoride and of the SMCL for protecting against cosmetic effects. Assessing the efficacy of fluoride in preventing dental caries is not covered in this report.

This chapter briefly reviews the sources of fluoride in drinking water, states the task the committee addressed, sets forth the committee’s activities and deliberative process in developing the report, and describes the organization of the report.

FLUORIDE IN DRINKING WATER

Fluoride may be found in drinking water as a natural contaminant or as an additive intended to provide public health protection from dental caries (artificial water fluoridation). EPA’s drinking water standards are restrictions on the amount of naturally occurring fluoride allowed in public water systems, and are not recommendations about the practice of water fluoridation. Recommendations for water fluoridation were established by the U.S. Public Health Service, and different considerations were factored into how those guidelines were established.

Natural

Fluoride occurs naturally in public water systems as a result of runoff from weathering of fluoride-containing rocks and soils and leaching from soil into groundwater. Atmospheric deposition of fluoride-containing emissions from coal-fired power plants and other industrial sources also contributes to amounts found in water, either by direct deposition or by deposition to soil and subsequent runoff into water. Of the approximately 10 million people with naturally fluoridated public water supplies in 1992, around 6.7 million had fluoride concentrations less than or equal to 1.2 mg/L (CDC 1993). Approximately 1.4 million had natural fluoride concentrations between 1.3 and 1.9 mg/L, 1.4 million had between 2.0 and 3.9 mg/L, and 200,000 had concentrations equal to or exceeding 4.0 mg/L. Exceptionally high concentrations of fluoride in drinking water are found in areas of Colorado (11.2 mg/L), Oklahoma (12.0 mg/L), New Mexico (13.0 mg/L), and Idaho (15.9 mg/L).

Areas of the United States with concentrations of fluoride in drinking water greater than 1.3 mg/L are all naturally contaminated. As discussed
below, a narrow concentration range of 0.7 to 1.2 mg/L is recommended when decisions are made to intentionally add fluoride into water systems. This lower range also occurs naturally in some areas of the United States. Information on the fluoride content of public water supplies is available from local water suppliers and local, county, or state health departments.

Artificial

Since 1945, fluoride has been added to many public drinking-water supplies as a public-health practice to control dental caries. The “optimal” concentration of fluoride in drinking water for the United States for the prevention of dental caries has been set at 0.7 to 1.2 mg/L, depending on the mean temperature of the locality (0.7 mg/L for areas with warm climates, where water consumption is expected to be high, and 1.2 mg/L for cool climates, where water consumption is low) (PHS 1991). The optimal range was determined by selecting concentrations that would maximize caries prevention and limit enamel fluorosis, a dose-related mottling of teeth that can range from mild discoloration of the surface to severe staining and pitting. Decisions about fluoridating a public drinking-water supply are made by state or local authorities. CDC (2002a) estimates that approximately 162 million people (65.8% of the population served by public water systems) received optimally fluoridated water in 2000.

The practice of fluoridating water supplies has been the subject of controversy since it began (see reviews by Nesin 1956; Wollan 1968; McClure 1970; Marier 1977; Hileman 1988). Opponents have questioned the motivation for and the safety of the practice; some object to it because it is viewed as being imposed on them by the states and as an infringement on their freedom of choice (Hileman 1988; Cross and Carton 2003). Others claim that fluoride causes various adverse health effects and question whether the dental benefits outweigh the risks (Colquhoun 1997). Another issue of controversy is the safety of the chemicals used to fluoridate water. The most commonly used additives are silicofluorides, not the fluoride salts used in dental products (such as sodium fluoride and stannous fluoride). Silicofluorides are one of the by-products from the manufacture of phosphate fertilizers. The toxicity database on silicofluorides is sparse and questions have been raised about the assumption that they completely dissociate in water and, therefore, have toxicity similar to the fluoride salts tested in laboratory studies and used in consumer products (Coplan and Masters 2001).

It also has been maintained that, because of individual variations in exposure to fluoride, it is difficult to ensure that the right individual dose to protect against dental caries is provided through large-scale water fluoridation. In addition, a body of information has developed that indicates
the major anticaries benefit of fluoride is topical and not systemic (Zero et al. 1992; Rölla and Ekstrand 1996; Featherstone 1999; Limeback 1999a; Clarkson and McLoughlin 2000; CDC 2001; Fejerskov 2004). Thus, it has been argued that water fluoridation might not be the most effective way to protect the public from dental caries.

Public health agencies have long disputed these claims. Dental caries is a common childhood disease. It is caused by bacteria that colonize on tooth surfaces, where they ferment sugars and other carbohydrates, generating lactic acid and other acids that decay tooth enamel and form a cavity. If the cavity penetrates to the dentin (the tooth component under the enamel), the dental pulp can become infected, causing toothaches. If left untreated, pulp infection can lead to abscess, destruction of bone, and systemic infection (Cawson et al. 1982; USDHHS 2000). Various sources have concluded that water fluoridation has been an effective method for preventing dental decay (Newbrun 1989; Ripa 1993; Horowitz 1996; CDC 2001; Truman et al. 2002). Water fluoridation is supported by the Centers for Disease Control and Prevention (CDC) as one of the 10 great public health achievements in the United States, because of its role in reducing tooth decay in children and tooth loss in adults (CDC 1999). Each U.S. Surgeon General has endorsed water fluoridation over the decades it has been practiced, emphasizing that “[a] significant advantage of water fluoridation is that all residents of a community can enjoy its protective benefit.... A person’s income level or ability to receive dental care is not a barrier to receiving fluoridation’s health benefits” (Carmona 2004).

As noted earlier, this report does not evaluate nor make judgments about the benefits, safety, or efficacy of artificial water fluoridation. That practice is reviewed only in terms of being a source of exposure to fluoride.

**HISTORY OF EPA’S REGULATION OF FLUORIDE**

In 1975, EPA proposed an interim primary drinking-water regulation for fluoride of 1.4-2.4 mg/L. That range was twice the “optimal” range of 0.7-1.2 mg/L recommended by the U.S. Public Health Service for water fluoridation. EPA’s interim guideline was selected to prevent the occurrence of objectionable enamel fluorosis, mottling of teeth that can be classified as mild, moderate, or severe. In general, mild cases involve the development of white opaque areas in the enamel of the teeth, moderate cases involve visible brown staining, and severe cases include yellow to brown staining and pitting and cracking of the enamel (NRC 1993). EPA considered objectionable enamel fluorosis to involve moderate to severe cases with dark stains and pitting of the teeth.

The history of EPA’s regulation of fluoride is documented in 50 Fed. Reg. 20164 (1985). In 1981, the state of South Carolina petitioned EPA...
to exclude fluoride from the primary drinking-water regulations and to set only an SMCL. South Carolina contended that enamel fluorosis should be considered a cosmetic effect and not an adverse health effect. The American Medical Association, the American Dental Association, the Association of State and Territorial Dental Directors, and the Association of State and Territorial Health Officials supported the petition. After reviewing the issue, the U.S. Public Health Service concluded there was no evidence that fluoride in public water supplies has any adverse effects on dental health, as measured by loss of teeth or tooth function. U.S. Surgeon General C. Everett Koop supported that position. The National Drinking Water Advisory Council (NDWAC) recommended that enamel fluorosis should be the basis for a secondary drinking-water regulation. Of the health effects considered to be adverse, NDWAC found osteosclerosis (increased bone density) to be the most relevant end point for establishing a primary regulation.

EPA asked the U.S. Surgeon General to review the available data on the nondental effects of fluoride and to determine the concentrations at which adverse health effects would occur and an appropriate margin of safety to protect public health. A scientific committee convened by the surgeon general concluded that exposure to fluoride at 5.0 to 8.0 mg/L was associated with radiologic evidence of osteosclerosis. Osteosclerosis was considered to be not an adverse health effect but an indication of osseous changes that would be prevented if the maximum content of fluoride in drinking water did not exceed 4 mg/L. The committee further concluded that there was no scientific documentation of adverse health effects at 8 mg/L and lower; thus, 4 mg/L would provide a margin of safety. In 1984, the surgeon general concluded that osteosclerosis is not an adverse health effect and that crippling skeletal fluorosis was the most relevant adverse health effect when considering exposure to fluoride from public drinking-water supplies. He continued to support limiting fluoride concentrations to 2 mg/L to avoid objectionable enamel fluorosis (50 Fed. Reg. 20164 [1985]).

In 1984, NDWAC took up the issue of whether psychological and behavioral effects from objectionable enamel fluorosis should be considered adverse. The council concluded that the cosmetic effects of enamel fluorosis could lead to psychological and behavioral problems that affect the overall well-being of the individual. EPA and the National Institute of Mental Health convened an ad hoc panel of behavioral scientists to further evaluate the potential psychological effects of objectionable enamel fluorosis. The panel concluded that “individuals who have suffered impaired dental appearance as a result of moderate or severe fluorosis are probably at increased risk for psychological and behavioral problems or difficulties” (R. E. Kleck, unpublished report, Nov. 17, 1984, as cited in 50 Fed. Reg. 20164 [1985]). NDWAC recommended that the primary drinking-water guideline for fluoride be set at 2 mg/L (50 Fed. Reg. 20164 [1985]).
On the basis of its review of the available data and consideration of the recommendations of various advisory bodies, EPA set an MCLG of 4 mg/L on the basis of crippling skeletal fluorosis (50 Fed. Reg. 47,142 [1985]). That value was calculated from an estimated lowest-observed-adverse-effect level of 20 mg/day for crippling skeletal fluorosis, the assumption that adult water intake is 2 L per day, and the application of a safety factor of 2.5. This factor was selected by EPA to establish an MCLG that was in agreement with a recommendation from the U.S. Surgeon General. In 1986, the MCL for fluoride was promulgated to be the same as the MCLG of 4 mg/L (51 Fed. Reg. 11,396 [1986]).

EPA also established an SMCL for fluoride of 2 mg/L to prevent objectionable enamel fluorosis in a significant portion of the population (51 Fed. Reg. 11,396 [1986]). To set that guideline, EPA reviewed data on the incidence of moderate and severe enamel fluorosis and found that, at a fluoride concentration of 2 mg/L, the incidence of moderate fluorosis ranged from 0% to 15%. Severe cases appeared to be observed only at concentrations above 2.5 mg/L. Thus, 2 mg/L was considered adequate for preventing enamel fluorosis that would be cosmetically objectionable. EPA established the SMCL as an upper boundary guideline for areas that have high concentrations of naturally occurring fluoride. EPA does not regulate or promote the addition of fluoride to drinking water. If fluoride in a community water system exceeds the SMCL but not the MCL, a notice about potential risk of enamel fluorosis must be sent to all customers served by the system (40 CFR 141.208[2005]).

In the early 1990s, the NRC was asked to independently review the health effects of ingested fluoride and EPA's MCL. The NRC (1993) found EPA's MCL of 4 mg/L to be an appropriate interim standard. Its report identified inconsistencies in the fluoride toxicity database and gaps in knowledge. Accordingly, the NRC recommended research in the areas of fluoride intake, enamel fluorosis, bone strength and fractures, and carcinogenicity. A list of the specific recommendations from that report is provided in Box 1-1.

COMMITTEE’S TASK

The Safe Drinking Water Act requires that EPA periodically review existing standards for water contaminants. Because of that requirement and new research on fluoride, EPA's Office of Water requested that the NRC reevaluate the adequacy of the MCLG and SMCL for fluoride to protect public health. The NRC assigned this task to the standing Committee on Toxicology, and convened the Committee on Fluoride in Drinking Water. The committee was asked to review toxicologic, epidemiologic, and clinical data, particularly data published since 1993, and exposure data on orally ingested fluoride from drinking water and other sources (e.g., food, tooth-
**Recommendations from NRC (1993) Report**

**Intake, Metabolism, and Disposition of Fluoride**
- Determine and compare intake of fluoride from all sources, including fluoride-containing dental products, in communities with fluoridated and nonfluoridated water. That information would improve our understanding of trends in dental caries, enamel fluorosis, and possibly other disorders or diseases.
- Determine the effects of factors that affect human acid-base balance and urinary pH on the metabolic characteristics, balance, and tissue concentrations of fluoride.
- Determine the metabolic characteristics of fluoride in infants, young children, and the elderly.
- Determine prospectively the metabolic characteristics of fluoride in patients with progressive renal disease.
- Using preparative and analytical methods now available, determine soft-tissue fluoride concentrations and their relation to plasma fluoride concentrations. Consider the relation of tissue concentrations to variables of interest, including past fluoride exposure and age.
- Identify the compounds that compose the “organic fluoride pool” in human plasma and determine their sources, metabolic characteristics, fate, and biological importance.

**Enamel Fluorosis**
- Identify sources of fluoride during the critical stages of tooth development in childhood and evaluate the contribution of each source to enamel fluorosis.
- Conduct studies on the relation between water fluoride concentrations and enamel fluorosis in various climatic zones.
- Determine the lowest concentration of fluoride in toothpaste that produces acceptable cariostasis.
- Conduct studies on the contribution of ingested fluoride and fluoride applied topically to teeth to prevent caries.

**Bone Fracture**
- Conduct a workshop to evaluate the advantages and disadvantages of the various doses, treatments, laboratory animal models, weight-bearing versus non-weight-bearing bones, and testing methods for bone strength that can be used to determine the effects of fluoride on bone.
- Conduct additional studies of hip and other fractures in geo-

*continued*
paste, dental rinses). On the basis of those reviews, the committee was asked to evaluate independently the scientific basis of EPA's MCLG of 4 mg/L and SMCL of 2 mg/L in drinking water and the adequacy of those guidelines to protect children and others from adverse health effects. The committee was asked to consider the relative contribution of various fluoride sources (e.g., food, dental-hygiene products) to total exposure. The committee also was asked to identify data gaps and make recommendations for future research relevant to setting the MCLG and SMCL for fluoride. Addressing questions of economics, risk-benefit assessment, and water-treatment technology was not part of the committee's charge.

The committee is aware that some readers expect this report to make a determination about whether public drinking-water supplies should be fluoridated. That expectation goes beyond the committee’s charge. As noted above, the MCLG and SMCL are guidelines for areas where fluoride con-
INTRODUCTION

centrations are naturally high. They are designed with the intent to protect the public from adverse health effects related to fluoride exposure and not as guidelines to provide health benefits.

COMMITTEE’S APPROACH

To accomplish its task, the committee held six meetings between August 2003 and June 2005. The first two meetings involved data-gathering sessions that were open to the public. The committee heard presentations from EPA, CDC, individuals involved in fluoride research, fluoridation supporters, and antifluoridation proponents. The committee also reviewed a large body of written material on fluoride, primarily focusing on research that was completed after publication of the 1993 NRC report. The available data included numerous research articles, literature reviews, position papers, and unpublished data submitted by various sources, including the public. Each paper and submission was evaluated case by case on its own merits.

Unless otherwise noted, the term fluoride is used in this report to refer to the inorganic, ionic form. Most of the nonepidemiologic studies reviewed involved exposure to a specified fluoride compound, usually sodium fluoride. Various units of measure are used to express exposure to fluoride in terms of exposure concentrations and internal dose (see Table 1-1 and Chapter 3). To the extent possible, the committee has tried to use units that allow for easy comparisons.

In this report, the committee updates information on the issues considered in the 1993 review—namely, data on pharmacokinetics; dental effects; skeletal effects; reproductive and developmental effects; neurological and behavioral effects; endocrine effects; gastrointestinal, renal, hepatic, and immune effects; genotoxicity; and carcinogenicity. More inclusive reviews are provided on effects to the endocrine and central nervous systems, because the previous NRC review did not give those effects as much attention. The committee used a general weight-of-evidence approach to evaluate the literature, which involved assessing whether multiple lines of evidence

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<th>Medium</th>
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<td>Water</td>
<td>1 ppm</td>
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<tr>
<td>Plasma</td>
<td>1 µmol/L</td>
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<td>Bone ash</td>
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<td>1%</td>
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ABBREVIATIONS: mg/kg, milligrams per kilogram; mg/L, milligrams per liter; µmol/L, micromoles per liter; ppm, parts per million.
indicate a human health risk. This included an evaluation of in vitro assays, animal research, and human studies (conducted in the United States and other countries). Positive and negative results were considered, as well as mechanistic and nonmechanistic information. The collective evidence was considered in perspective with exposures likely to occur from fluoride in drinking water at the MCLG or SMCL.

In evaluating the effects of fluoride, consideration is given to the exposure associated with the effects in terms of dose and time. Dose is a simple variable (such as mg/kg/day), and time is a complex variable because it involves not only the frequency and duration of exposure but also the persistence of the agent in the system (kinetics) and the effect produced by the agent (dynamics). Whether the key rate-limiting events responsible for the adverse effect are occurring in the kinetic or in the dynamic pathway is important in understanding the toxicity of a chemical and in directing future research (see Rozman and Doull 2000). The committee also attempts to characterize fluoride exposures from various sources to different subgroups within the general population and to identify subpopulations that might be particularly susceptible to the effects of fluoride.

**STRUCTURE OF THE REPORT**

The remainder of this report is organized into 10 chapters. Chapter 2 characterizes the general public’s exposure to fluoride from drinking water and other sources. Chapter 3 provides a description of the chemistry of fluoride and pharmacokinetic information that was considered in evaluating the toxicity data on fluoride. In Chapters 4-9, the committee evaluates the scientific literature on adverse effects of fluoride on teeth, the musculoskeletal system, reproduction and development, the nervous system, the endocrine system, the gastrointestinal system, the kidneys, the liver, and the immune system. Chapter 10 evaluates the genotoxic and carcinogenic potential of fluoride. Finally, Chapter 11 provides an assessment of the most significant health risks from fluoride in drinking water and its implications for the adequacy of EPA’s MCLG and SMCL for protecting the public.
Measures of Exposure to Fluoride in the United States

The major sources of internal exposure of individuals to fluorides are the diet (food, water, beverages) and fluoride-containing dental products (toothpaste, fluoride supplements). Internal exposure to fluorides also can occur from inhalation (cigarette smoke, industrial emissions), dermal absorption (from chemicals or pharmaceuticals), ingestion or parenteral administration of fluoride-containing drugs, and ingestion of fluoride-containing soil. Information on the pharmacokinetics of fluoride are provided in Chapter 3.

The National Research Council’s (NRC’s) 1993 review of the health effects of ingested fluoride reported estimates of average daily fluoride intake from the diet of 0.04-0.07 milligrams per kilogram (mg/kg) of body weight for young children in an area with fluoridated water (fluoride concentration in drinking water, 0.7-1.2 mg per liter [L]; NRC 1993). Dietary intake of fluoride by adults in an area with fluoridated water was variously estimated to be between 1.2 and 2.2 mg/day (0.02-0.03 mg/kg for a 70-kg adult). The fluoride intake from toothpaste or mouth rinse by children with good control of swallowing, assuming twice-a-day use, was estimated to equal the intake from food, water, and beverages. The review acknowledged that “substantially” higher intakes of fluoride from consumption of fluoridated water would result for individuals such as outdoor laborers in warm climates or people with high-urine-output disorders, but these intakes were not quantified. Similarly, children and others with poor control of swallowing could have intakes of fluoride from dental products that exceed the dietary intakes, but these intakes also were not quantified. Other factors cited as affecting individual fluoride intakes include changes in the guidelines for
fluoride supplementation and use of bottled water or home water purification systems rather than fluoridated municipal water. The NRC (1993) recommended further research to “determine and compare the intake of fluoride from all sources, including fluoride-containing dental products, in fluoridated and nonfluoridated communities.”

This chapter provides a review of the available information on fluoride exposures in the United States, including sources of fluoride exposure, intakes from various fluoride sources, and factors that could affect individual exposures to fluorides. Population subgroups with especially high exposures are discussed. The major emphasis of this chapter is on chronic exposure rather than acute exposure. The use of biomarkers as alternative approaches to estimation of actual individual exposures is also discussed.

In practice, most fluorine added to drinking water is in the form of fluosilicic acid (fluorosilicic acid, H$_2$SiF$_6$) or the sodium salt (sodium fluosilicate, Na$_2$SiF$_6$), collectively referred to as fluorsilicates (CDC 1993); for some smaller water systems, fluoride is added as sodium fluoride (NaF). Fluoride in toothpaste and other dental products is usually present as sodium fluoride (NaF), stannous fluoride (SnF$_2$), or disodium monofluorophosphate (Na$_2$PO$_3$F). Fluorine-containing pesticides and pharmaceuticals also contribute to total fluorine exposures and are considered separately. Fluoride in food and drinking water usually is considered in terms of total fluorine content, assumed to be present entirely as fluoride ion (F$^-$. Information on exposures to fluorsilicates and aluminofluorides is also included.

**SOURCES OF FLUORIDE EXPOSURE**

**Drinking Water**

**General Population**

The major dietary source of fluoride for most people in the United States is fluoridated municipal (community) drinking water, including water consumed directly, food and beverages prepared at home or in restaurants from municipal drinking water, and commercial beverages and processed foods originating from fluoridated municipalities. On a mean per capita basis, community (public or municipal) water constitutes 75% of the total water ingested in the United States; bottled water constitutes 13%, and other sources (e.g., wells and cisterns) constitute 10% (EPA 2000a). Municipal water sources that are not considered “fluoridated” could contain low concentrations of naturally occurring fluoride, as could bottled water and private wells, depending on the sources.

An estimated 162 million people in the United States (65.8% of the population served by public water systems) received “optimally fluori-
dated” water in 2000 (CDC 2002a). This represents an increase from 144 million (62.1%) in 1992. The total number of people served by public water systems in the United States is estimated to be 246 million; an estimated 35 million people obtain water from other sources such as private wells (CDC 2002a,b). The U.S. Environmental Protection Agency (EPA) limits the fluoride that can be present in public drinking-water supplies to 4 mg/L (maximum contaminant level, or MCL) to protect against crippling skeletal fluorosis, with a secondary maximum contaminant level (SMCL) of 2 mg/L to protect against objectionable enamel fluorosis (40CFR 141.62(b)[2001], 40CFR 143.3[2001]).

Of the 144 million people with fluoridated public water supplies in 1992, approximately 10 million (7%) received naturally fluoridated water, the rest had artificially fluoridated water (CDC 2002c). Of the population with artificially fluoridated water in 1992, more than two-thirds had a water fluoride concentration of 1.0 mg/L, with almost one-quarter having lower concentrations and about 5% having concentrations up to 1.2 mg/L (CDC 1993; see Appendix B).

Of the approximately 10 million people with naturally fluoridated public water supplies in 1992, approximately 67% had fluoride concentrations ≤ 1.2 mg/L (CDC 1993; see Appendix B). Approximately 14% had fluoride concentrations between 1.3 and 1.9 mg/L and another 14% had between 2.0 and 3.9 mg/L; 2% (just over 200,000 persons) had natural fluoride concentrations equal to or exceeding 4.0 mg/L.2 Water supplies that exceeded 4.0 mg/L ranged as high as 11.2 mg/L in Colorado, 12.0 mg/L in Oklahoma, 13.0 mg/L in New Mexico, and 15.9 mg/L in Idaho (see Appendix B, Table B-3).3 States with the largest populations receiving water supplies with fluoride at ≥ 4.0 mg/L included Virginia (18,726 persons, up to 6.3 mg/L), Oklahoma (18,895 persons, up to 12.0 mg/L), Texas (36,863 persons, up to 8.8 mg/L), and South Carolina (105,618 persons, up to 5.9 mg/L).

Little information is available on the fluoride content of private water sources, but the variability can reasonably be expected to be high and to

1The term optimally fluoridated water means a fluoride level of 0.7-1.2 mg/L; water fluoride levels are based on the average maximum daily air temperature of the area (see Appendix B).

2More recently (2000), CDC has estimated that 850,000 people are served by public water supplies containing fluoride in excess of 2 mg/L; of these, 152,000 people receive water containing fluoride in excess of 4 mg/L (unpublished data from CDC as reported in EPA 2003a). Based on analytical data from 16 states, EPA (2003a) estimates that 1.5-3.3 million people nationally are served by public water supplies with fluoride concentrations exceeding 2 mg/L; of these 118,000-301,000 people receive water with fluoride concentrations greater than 4 mg/L.

3High-fluoride municipal waters are generally found in regions that have high fluoride concentrations in the groundwater or in surface waters. ATSDR (2003) has reviewed fluoride concentrations in environmental media, including groundwater and surface water. Fleischer (1962) and Fleischer et al. (1974) reported fluoride concentrations in groundwater by county for the coterminous United States.
depend on the region of the country. Fluoride measured in well water in one study in Iowa ranged from 0.06 to 7.22 mg/L (mean, 0.45 mg/L); home-filtered well water contained 0.02-1.00 mg/L (mean, 0.32 mg/L; Van Winkle et al. 1995). Hudak (1999) determined median fluoride concentrations for 237 of 254 Texas counties (values were not determined for counties with fewer than five observations). Of the 237 counties, 84 have median groundwater fluoride concentrations exceeding 1 mg/L; of these, 25 counties exceed 2 mg/L and five exceed 4 mg/L. Residents in these areas (or similar areas in other states) who use groundwater from private wells are likely to exceed current guidelines for fluoride intake.

Duperon et al. (1995) pointed out that fluoride concentrations reported by local water suppliers can be substantially different from concentrations measured in water samples obtained in homes. Use of home water filtration or purification systems can reduce the fluoride concentration in community water by 13% to 99%, depending on the type of system (Duperon et al. 1995; Van Winkle et al. 1995; Jobson et al. 2000). Distillation or reverse osmosis can remove nearly all the fluoride. The extent of use of home water filtration or purification systems nationally is not known but obviously would affect the fluoride intake for people using such systems. Van Winkle et al. (1995) reported that 11% of their study population (in Iowa) used some type of home filtration either for well water or for public water.

Fluoride concentrations in bottled water\(^4\) are regulated by law to a maximum of 1.4-2.4 mg/L if no fluoride is added and a maximum of 0.8-1.7 mg/L if fluoride is added (the applicable value within the range depends on the annual average of maximum daily air temperatures at the location of retail sale; 21CFR 165.110[2003]). Maximum fluoride concentrations for imported bottled water are 1.4 mg/L if no fluoride is added and 0.8 mg/L if fluoride is added (21CFR 165.110[2003]). Fluoride concentrations are required on labels in the United States only if fluoride is added. Fluoride concentrations listed on labels or in chemical analyses available on the Internet for various brands range from 0 to 3.6 mg/L (Bartels et al. 2000; Johnson and DeBiase 2003; Bottled Water Web 2004); of those without added fluoride, most are below 0.6 mg/L. Most brands appear to list fluoride content only if they are specifically advertising the fact that their water is fluoridated; fluoride concentrations of these brands range from 0.5 to 0.8 mg/L (for “nursery” or “infant” water) up to 1.0 mg/L. Several reports indicate

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\(^4\)The term “bottled water” applies to water intended for human consumption, containing no added ingredients besides fluoride or appropriate antimicrobial agents; the regulations apply to bottled water, drinking water, artesian water, artesian well water, groundwater, mineral water, purified water, demineralized water, deionized water, distilled water, reverse osmosis water, purified drinking water, demineralized drinking water, deionized drinking water, distilled drinking water, reverse osmosis drinking water, sparkling water, spring water, and well water (21CFR 165.110[2003]).
that fluoride concentrations obtained from the manufacturer or stated on labels for bottled waters might not be accurate (Weinberger 1991; Toumba et al. 1994; Bartels et al. 2000; Lalumandier and Ayers 2000; Johnson and DeBiase 2003; Zohouri et al. 2003).

Measured fluoride concentrations in bottled water sold in the United States have varied from 0 to 1.36 mg/L (Nowak and Nowak 1989; Chan et al. 1990; Stannard et al. 1990; Van Winkle et al. 1995; Bartels et al. 2000; Lalumandier and Ayers 2000; Johnson and DeBiase 2003). Van Winkle et al. (1995) reported a mean of 0.18 mg/L for 78 commercial bottled waters in Iowa. Johnson and DeBiase (2003) more recently reported values ranging from 0 to 1.2 mg/L for 65 bottled waters purchased in West Virginia, with 57 brands having values below 0.6 mg/L. Measured fluoride concentrations in bottled waters in other countries have similar ranges: 0.05-4.8 mg/L in Canada (Weinberger 1991), 0.10-0.80 mg/L in the United Kingdom (Toumba et al. 1994), and 0.01-0.37 mg/L more recently in the United Kingdom (Zohouri et al. 2003). Bartels et al. (2000) found significant variation in fluoride concentrations among samples of the same brand with different bottling dates purchased in the same city. In general, distilled and purified (reverse osmosis) waters contain very low concentrations of fluoride; drinking water (often from a municipal tap) and spring water vary with their source, as do mineral waters, which can be very low or very high in fluoride. Most spring water sold in the United States probably has a low fluoride content (<0.3 mg/L). Typical fluoride concentrations in various types of drinking water in the United States are summarized in Table 2-1.

Average per capita ingestion of community or municipal water is estimated to be 927 mL/day (EPA 2000a; see Appendix B). The estimated 90th percentile of the per capita ingestion of community water from that survey is 2.016 L/day. Estimated intakes by those actually consuming community water (excluding people with zero ingestion of community water) are higher, with a mean of 1.0 L/day and a 90th percentile of 2.069 L/day (EPA 2000a). Thus, if national estimates of water intake (see Appendix B)

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5 The European Commission has set a maximum limit of 5.0 mg/L for fluoride in natural mineral waters, effective January 1, 2008 (EC 2003). In addition, natural mineral waters with a fluoride concentration exceeding 1.5 mg/L must be labeled with the words “contains more than 1.5 mg/L of fluoride: not suitable for regular consumption by infants and children under 7 years of age,” and for all natural mineral waters, the actual fluoride content is to be listed on the label. England has essentially the same requirements (TSO 2004), applicable to all bottled waters (natural mineral waters, spring water, and bottled drinking water).

6 As described more fully in Appendix B, the values from EPA (2000a) are from a short-term survey of more than 15,000 individuals in the United States. Although these values are considered reasonable indicators both of typical water consumption and of the likely range of water consumption on a long-term basis, they should not be used by themselves to predict the number of individuals or percentage of the population that consumes a given amount of water on a long-term basis.
TABLE 2-1 Typical Fluoride Concentrations of Major Types of Drinking Water in the United States

<table>
<thead>
<tr>
<th>Source</th>
<th>Range, mg/L&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Municipal water (fluoridated)</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td>Municipal water (naturally fluoridated)</td>
<td>0.7-4.0+</td>
</tr>
<tr>
<td>Municipal water (nonfluoridated)</td>
<td>&lt;0.7</td>
</tr>
<tr>
<td>Well water</td>
<td>0-7+</td>
</tr>
<tr>
<td>Bottled water from municipal source</td>
<td>0-1.2</td>
</tr>
<tr>
<td>Spring water</td>
<td>0-1.4 (usually &lt;0.3)</td>
</tr>
<tr>
<td>Bottled “infant” or “nursery” water</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Bottled water with added fluoride&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Distilled or purified water</td>
<td>&lt;0.15</td>
</tr>
</tbody>
</table>

<sup>a</sup>See text for relevant references.

<sup>b</sup>Other than “infant” or “nursery” water.

are assumed to be valid for the part of the population with fluoridated water supplies, the intake of fluoride for a person with average consumption of community water (1 L/day) in a fluoridated area ranges from 0.7 to 1.2 mg/day, depending on the area. A person with consumption of community water equivalent to the 90th percentile in that survey (2.069 L/day) would have a fluoride intake between 1.4 and 2.5 mg/day, from community water alone. Table 2-2 provides examples of fluoride intake by typical and high consumers of municipal water by age group.

The estimates of water consumption described in Appendix B are in keeping with recently published “adequate intake” values for total water consumption (including drinking water, all beverages, and moisture in food; IOM 2004; see Appendix B, Table B-10). Note that these estimates are national values; the range of values for optimal fluoridation was intended to account for expected regional differences in water consumption due to regional temperature differences (see Appendix B). A separate study based on the same data used by EPA (2000a) found no strong or consistent association between water intake and month or season (Heller et al. 1999). Another recent study of American children aged 1-10 years also found no significant relationship between water consumption and mean temperature in modern conditions (perhaps due to artificial temperature regulation) and suggested that the temperature-related guidelines for fluoride concentrations in drinking water be reevaluated (Sohn et al. 2001).

Actual intakes of fluoride from drinking water by individuals depend on their individual water intakes, the source or sources of that water, and the use of home water purification or filtration systems. As described earlier, fluoride concentrations in community water might vary from their reported concentrations; fluoride content of bottled water also varies considerably with brand or source, with packaging date for a given brand, and from
### TABLE 2-2 Examples of Fluoride Intake from Consumption of Community (Municipal) Water by People Living in Fluoridated Areas

<table>
<thead>
<tr>
<th></th>
<th>Typical Consumers&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Fluoride Intake&lt;sup&gt;d&lt;/sup&gt;</th>
<th>High Consumers&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Fluoride Intake&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water Consumption</td>
<td>Fluoride Intake</td>
<td>Water Consumption</td>
<td>Fluoride Intake</td>
</tr>
<tr>
<td></td>
<td>mL/day</td>
<td>mL/kg/day</td>
<td>mg/day</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>U.S. population (total)</td>
<td>1,000</td>
<td>17</td>
<td>0.7-1.2</td>
<td>0.012-0.020</td>
</tr>
<tr>
<td>All infants (&lt;1 year)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>500</td>
<td>60</td>
<td>0.35-0.6</td>
<td>0.042-0.072</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>350</td>
<td>26</td>
<td>0.25-0.42</td>
<td>0.018-0.031</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>450</td>
<td>23</td>
<td>0.32-0.54</td>
<td>0.016-0.028</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>500</td>
<td>16</td>
<td>0.35-0.6</td>
<td>0.011-0.019</td>
</tr>
<tr>
<td>Youths 13-19 years</td>
<td>800</td>
<td>12</td>
<td>0.56-0.96</td>
<td>0.0084-0.014</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>1,100</td>
<td>16</td>
<td>0.77-1.3</td>
<td>0.011-0.019</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>1,200</td>
<td>17</td>
<td>0.84-1.4</td>
<td>0.012-0.020</td>
</tr>
<tr>
<td>Females 13-49 years&lt;sup&gt;f&lt;/sup&gt;</td>
<td>980</td>
<td>15</td>
<td>0.69-1.2</td>
<td>0.011-0.018</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on consumption data described in Appendix B for people actually consuming community (municipal) water.

<sup>b</sup>Based on a typical consumption rate of community (municipal) water for the age group.

<sup>c</sup>Based on a reasonably high (but not upper bound) consumption rate of community (municipal) water for the age group; some individual exposures could be higher.

<sup>d</sup>Based on fluoride concentrations of 0.7-1.2 mg/L.

<sup>e</sup>Includes any infant, nursing or nonnursing, who consumes at least some community water; these infants may be fed primarily breast milk, ready-to-feed formula (to which no water is normally added), or formula prepared from concentrate (which requires addition of water).

<sup>f</sup>Women of childbearing age.
information (if any) given on the labels or provided by the manufacturer. Private water sources (e.g., wells and cisterns) probably are even more variable in fluoride content, with some regions of the country being especially high and others very low. A number of authors have pointed out the difficulty doctors and dentists face in ascertaining individual fluoride intakes, just from drinking water (from all sources), for the purpose of prescribing appropriate fluoride supplementation (Nowak and Nowak 1989; Chan et al. 1990; Stannard et al. 1990; Levy and Shavlick 1991; Weinberger 1991; Dillenberg et al. 1992; Jones and Berg 1992; Levy and Muchow 1992; Toumba et al. 1994; Duperon et al. 1995; Van Winkle et al. 1995; Heller et al. 1999; Bartels et al. 2000; Lalumandier and Ayers 2000; Johnson and DeBiase 2003; Zohouri et al. 2003).

High Intake Population Subgroups

EPA, in its report to Congress on sensitive subpopulations (EPA 2000b), defines sensitive subpopulations in terms of either their response (more severe response or a response to a lower dose) or their exposure (greater exposure than the general population). Hence, it is appropriate to consider those population subgroups whose water intake is likely to be substantially above the national average for the corresponding sex and age group. These subgroups include people with high activity levels (e.g., athletes, workers with physically demanding duties, military personnel); people living in very hot or dry climates, especially outdoor workers; pregnant or lactating women; and people with health conditions that affect water intake. Such health conditions include diabetes mellitus, especially if untreated or poorly controlled; disorders of water and sodium metabolism, such as diabetes insipidus; renal problems resulting in reduced clearance of fluoride; and short-term conditions requiring rapid rehydration, such as gastrointestinal upsets or food poisoning (EPA 2000a). (While the population sample described in Appendix B [Water Ingestion and Fluoride Intakes] included some of these individuals, the study did not attempt to estimate means or distributions of intake for these specific subgroups.)

As shown in Appendix B (Tables B-4 to B-9), some members of the U.S. population could have intakes from community water sources of as much as 4.5-5 L/day (as high as 80 mL/kg/day for adults). Some infants have intakes of community water exceeding 200 mL/kg/day. Heller et al. (1999), using the same data set as EPA (2000a), reported that 21 of 14,640 people (of all ages) had water intakes over 6 standard deviations from the mean (greater than 249 mL/kg/day). Whyte et al. (2005) describe an adult woman who consistently consumed 1-2 gallons (3.8-7.6 L) of fluid per day (instant tea made with well water); no specific reason for her high fluid consumption is given.
Fluid requirements of athletes, workers, and military personnel depend on the nature and intensity of the activity, the duration of the activity, and the ambient temperature and humidity. Total sweat losses for athletes in various sports can range from 200 to 300 mL/hour to 2,000 mL/hour or more (Convertino et al. 1996; Horswill 1998; Cox et al. 2002; Coyle 2004). Most recommendations on fluid consumption for athletes are concerned with matching fluid replacement to fluid losses during the training session or competition to minimize the detrimental effects of dehydration on athletic performance (Convertino et al. 1996; Horswill 1998; Coris et al. 2004; Coyle 2004). Depending on the nature of the sport or training session, the ease of providing fluid, and the comfort of the athlete with respect to content of the gastrointestinal tract, fluid intake during exercise is often only a fraction (e.g., one-half) of the volume lost, and losses of 2% of body weight or more might occur during an exercise session in spite of fluid consumption during the session (Convertino et al. 1996; Cox et al. 2002; Coris et al. 2004; Coyle 2004).

Total daily fluid consumption by athletes generally is not reported; for many athletes, it is probably on the order of 5% of body weight (50 mL/kg/day) or more to compensate for urinary and respiratory losses as well as sweat losses. For example, Crossman (2003) described a professionally prepared diet plan for a major league baseball player that includes 26 cups (6.2 L) of water or sports drink on a workout day and 19 cups (4.5 L) on an off-day; this is in addition to 9-11 cups (2.1-2.6 L) of milk, fruit juice, and sports drink with meals and scheduled snacks (total fluid intake of 6.8-8.8 L/day, or 52-67 mL/kg/day for a 132-kg player\(^7\)). While some players and teams probably use bottled or distilled water, most (especially at the amateur and interscholastic levels) probably use local tap water; also, sports drinks might be prepared (commercially or by individuals) with tap water.

The U.S. Army’s policy on fluid replacement for warm-weather training calls for 0.5-1 quart/hour (0.47-0.95 L/hour), depending on the temperature, humidity, and type of work (Kolka et al. 2003; USASMA 2003). In addition, fluid intake is not to exceed 1.5 quarts/hour (1.4 liter/hour) or 12 quarts/day (11.4 L/day). The Army’s planning factor for individual tap water consumption ranges from 1.5 gallons/day (5.7 L/day) for temperate conditions to 3.0 gallons/day (11.4 L/day) for hot conditions (U.S. Army 1983). Hourly intake can range from 0.21 to 0.65 L depending on the temperature (McNall and Schlegel 1968), and daily intake among physically active individuals can range from 6 to 11 L (U.S. Army 1983, cited by EPA 1997). Nonmilitary outdoor workers in hot or dry climates probably would have similar needs.

\(^7\)The player’s weight was obtained from the 2003 roster of the Cleveland Indians baseball team (http://cleveland.indians.mlb.com).
Water intakes for pregnant and lactating women are listed separately in Appendix B (Tables B-4 to B-9). Total water intake for pregnant women does not differ greatly from that for all adult females (Table B-9), while total water consumption by lactating women is generally higher. For the highest consumers among lactating women, consumption rates approximate those for athletes and workers (50-70 mL/kg/day).

Diabetes mellitus and diabetes insipidus are both characterized by high water intakes and urine volumes, among other things (Beers and Berkow 1999; Eisenbarth et al. 2002; Robinson and Verbalis 2002; Belchetz and Hammond 2003). People with untreated or poorly controlled diabetes mellitus would be expected to have substantially higher fluid intakes than nondiabetic members of the population. The American Diabetes Association (2004) estimates that 18.2 million people in the United States (6.3% of the population) have diabetes mellitus and that 5.2 million of these are not aware they have the disease. Other estimates range from 16 to 20 million people in the United States, with up to 50% undiagnosed (Brownlee et al. 2002; Buse et al. 2002).

Diabetes insipidus, or polyuria, is defined as passage of large volumes of urine, in excess of about 2 L/m²/day (approximately 150 mL/kg/day at birth, 110 mL/kg/day at 2 years, and 40 mL/kg/day in older children and adults) (Baylis and Cheetham 1998; Cheetham and Baylis 2002). Diabetes insipidus includes several types of disease distinguished by cause, including both familial and acquired disorders (Baylis and Cheetham 1998; Cheetham and Baylis 2002; Robinson and Verbalis 2002). Water is considered a therapeutic agent for diabetes insipidus (Beers and Berkow 1999; Robinson and Verbalis 2002); in addition, some kinds of diabetes insipidus can be treated by addressing an underlying cause or by administering vasopressin (antidiuretic hormone) or other agents to reduce polyuria to a tolerable level. The Diabetes Insipidus Foundation (2004) estimates the number of diabetes insipidus patients in the United States at between 40,000 and 80,000.

Someone initially presenting with central or vasopressin-sensitive diabetes insipidus might ingest “enormous” quantities of fluid and may produce 3-30 L of very dilute urine per day (Beers and Berkow 1999) or up to 400 mL/kg/day (Baylis and Cheetham 1998). Most patients with central diabetes insipidus have urine volumes of 6-12 L/day (Robinson and Verbalis 2002). Patients with primary polydipsia might ingest and excrete up to 6 L of fluid per day (Beers and Berkow 1999). Pivonello et al. (1998) listed water intakes of 5.5-8.6 L/day for six adults with diabetes insipidus who did not take vasopressin and 1.4-2.5 L/day for 12 adults who used a vasopressin analogue. An estimated 20% to 40% of patients on lithium therapy have a urine volume > 2.5 L/day, and up to 12% have frank nephrogenic diabetes insipidus characterized by a urine volume > 3 L/day (Mukhopadhyay et al. 2001).
Five papers described enamel fluorosis in association with diabetes insipidus or polydipsia (Table 2-3). Two of the papers described cases of enamel fluorosis in the United States resulting from fluoride concentrations of 1, 1.7, or 2.6 mg/L in drinking water (Juncos and Donadio 1972; Greenberg et al. 1974). The two individuals drinking water with fluoride at 1.7 and 2.6 mg/L also had roentgenographic bone changes consistent with “systemic fluorosis” (Juncos and Donadio 1972). These patients and four other renal patients in the U.S. “in whom fluoride may have been the cause of detectable clinical and roentgenographic effects” were also reported by Johnson et al. (1979); most of the patients had urine volumes exceeding 3 L/day and drinking water with fluoride concentrations around 1.7-3 mg/L.

Moderate and severe enamel fluorosis have been reported in diabetes insipidus patients in other countries with drinking water containing fluoride at 0.5 mg/L (Klein 1975) or 1 mg/L (Seow and Thomsett 1994), and severe enamel fluorosis with skeletal fluorosis has been reported with fluoride at 3.4 mg/L (Mehta et al. 1998). Greenberg et al. (1974) recommended that children with any disorder that gives rise to polydipsia and polyuria be supplied a portion of their water from a nonfluoridated source.

Table 2-4 provides examples of fluoride intake by members of several population subgroups characterized by above-average water consumption (athletes and workers, patients with diabetes mellitus or diabetes insipidus). It should be recognized that, for some groups of people with high water intakes (e.g., those with a disease condition or those playing indoor sports such as basketball or hockey), there probably will be little correlation of water intake with outdoor temperature—such individuals in northern states would consume approximately the same amounts of water as their counterparts in southern states. However, fluoridation still varies from state to state (Appendix B), so that some individuals could consume up to 1.7 times as much as others for the same water intake (1.2 versus 0.7 mg/L).

### Background Food

Measured fluoride in samples of human breast milk is very low. Dabeka et al. (1986) found detectable concentrations in only 92 of 210 samples (44%) obtained in Canada, with fluoride ranging from <0.004 to 0.097 mg/L. The mean concentration in milk from mothers in fluoridated

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8These two individuals also had impaired renal function, which could have increased their retention of fluoride (see Chapter 3).

9Greenberg et al. (1974) listed “central diabetes insipidus, psychogenic water ingestion, renal medullary disease, including hypercalcaemic nephropathy, hypokalaemic nephropathy and anatomic and vascular disturbances and those diseases causing solute diuresis” as disorders associated with “excessive” consumption of water and therefore the possibility of “fluoride toxicity in a community with acceptable fluoride concentration.”
<table>
<thead>
<tr>
<th>Study Subjects</th>
<th>Exposure Conditions</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 18-year-old boy, 57.4 kg</td>
<td>(a) “high” intake of well water containing fluoride at 2.6 mg/L since early childhood; current intake, 7.6 L/day (0.34 mg/kg/day)</td>
<td>Enamel fluorosis and roentgenographic bone changes consistent with “systemic fluorosis,” attributed to the combination of renal insufficiency and polydipsia (the latter resulting from the renal disease); reported by the Mayo Clinic</td>
<td>Juncos and Donadio 1972</td>
</tr>
<tr>
<td>(b) 17-year-old girl, 45.65 kg (United States)</td>
<td>(b) “high” intake of water containing fluoride at 1.7 mg/L since infancy; current intake, 4 L/day (0.15 mg/kg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 boys (ages 10 and 11) with familial nephrogenic diabetes insipidus (United States)</td>
<td>Fluoridated communities in the U.S. (1 mg/L); one child since birth, one since age 4; fluid intake ranged from 2.6 to 6 times normal daily intake for age (approximately 1.25-3 L/day at time of study)</td>
<td>Enamel fluorosis; fluoride concentrations in deciduous teeth (enamel layer 50-100 µm from surface) 3-6 times those in controls (normal boys aged 10-14 residing in an area with fluoride at 1 mg/L)</td>
<td>Greenberg et al. 1974</td>
</tr>
<tr>
<td>Mother and four children with familial pituitary diabetes insipidus (Israel)</td>
<td>Water had “lower than accepted” fluoride content (0.5 mg/L); water consumption by mother and two teenage daughters (none used vasopressin) was 10-15 L/day each; two younger children treated for diabetes insipidus from ages 3 and 5</td>
<td>Enamel fluorosis in all four children: severe in the older two who were not treated for diabetes insipidus, milder in the two younger children who were treated for diabetes insipidus. Mother also had diabetes insipidus and fluorosis; she had grown up in Kurdistan with an unknown water fluoride content</td>
<td>Klein 1975</td>
</tr>
<tr>
<td>Six cases of familial pituitary diabetes insipidus (Australia)</td>
<td>Children had average water intake of 8-10 L/day; two of the children lived in fluoridated areas (1 mg/L)</td>
<td>Moderate (one child) or severe (one child) enamel fluorosis in the two children who lived in fluoridated areas</td>
<td>Seow and Thomsett 1994</td>
</tr>
<tr>
<td>Two brothers with pituitary diabetes insipidus (ages 17 and 7) (India)</td>
<td>Well water with fluoride at 3.4 mg/L</td>
<td>Severe enamel fluorosis, skeletal deformities, and radiological evidence of skeletal fluorosis</td>
<td>Mehta et al. 1998</td>
</tr>
</tbody>
</table>

TABLE 2-3 Case Reports of Fluorosis in Association with Diabetes Insipidus or Polydipsia
### TABLE 2-4 Examples of Fluoride Intake from Drinking Water by Members of Selected Population Subgroups Living in Fluoridated Areas\(^a\)

<table>
<thead>
<tr>
<th>Population Subgroup (Weight)</th>
<th>Typical Consumers(^b)</th>
<th>High Consumers(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water Consumption</td>
<td>Fluoride Intake(^d)</td>
</tr>
<tr>
<td></td>
<td>mL/day</td>
<td>mL/kg/day</td>
</tr>
<tr>
<td>Athletes, workers, military (50 kg)</td>
<td>2,500</td>
<td>50</td>
</tr>
<tr>
<td>Athletes, workers, military (70 kg)</td>
<td>3,500</td>
<td>50</td>
</tr>
<tr>
<td>Athletes, workers, military (100 kg)</td>
<td>5,000</td>
<td>50</td>
</tr>
<tr>
<td>Athletes and workers (120 kg)</td>
<td>6,000</td>
<td>50</td>
</tr>
<tr>
<td>DM patients (20 kg)</td>
<td>1,000</td>
<td>50</td>
</tr>
<tr>
<td>DM patients (70 kg)</td>
<td>3,500</td>
<td>50</td>
</tr>
<tr>
<td>NDI patients (20 kg)</td>
<td>1,000</td>
<td>50</td>
</tr>
<tr>
<td>NDI patients (70 kg)</td>
<td>3,500</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^a\)Assumes all drinking water is from fluoridated community (municipal) sources.

\(^b\)Based on a typical consumption rate for the population subgroup.

\(^c\)Based on a reasonably high (but not upper bound) consumption rate for the population subgroup; some individual exposures could be higher.

\(^d\)Based on fluoride concentrations of 0.7-1.2 mg/L.

**ABBREVIATIONS:** DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.
communities (1 mg/L in the water) was 0.0098 mg/L; in nonfluoridated communities, the mean was 0.0044 mg/L). Fluoride concentrations were correlated with the presence of fluoride in the mother’s drinking water. Spak et al. (1983) reported mean fluoride concentrations in colostrum of 0.0053 mg/L (0.28 µM/L) in an area in Sweden with fluoride at 0.2 mg/L in drinking water and 0.0068 mg/L (0.36 µM/L) in an area with fluoride at 1.0 mg/L in the drinking water; in the fluoridated area, the mean fluoride concentration in mature milk was 0.007 mg/L (0.37 µM/L). No statistically significant difference in milk fluoride concentration between the two areas was found.

Hossny et al. (2003) reported fluoride concentrations in breast milk of 60 mothers in Cairo, Egypt, ranging from 0.002 to 0.01 mg/L [0.1-0.6 µM/L; median, 0.0032 mg/L (0.17 µM/L); mean, 0.0046 mg/L (0.24 µM/L)]. Cairo is considered nonfluoridated, with a reported water fluoride concentration of 0.3 mg/L (Hossny et al. 2003). Opinya et al. (1991) found higher fluoride concentrations in mothers’ milk (mean, 0.033 mg/L; range, 0.011-0.073 mg/L), but her study population was made up of mothers in Kenya with an average daily fluoride intake of 22.1 mg. However, even at very high fluoride intakes by mothers, breast milk still contains very low concentrations of fluoride compared with other dietary fluoride sources. No significant correlation was established between the fluoride in milk and the intake of fluoride in the Kenyan study (Opinya et al. 1991).

Cows’ milk likewise contains very low fluoride concentrations, compared with other dietary sources such as drinking water. Dairy milk samples measured in Houston contained fluoride at 0.007 to 0.068 mg/L (average, 0.03 mg/L) (Liu et al. 1995). Milk samples in 11 Canadian cities contained 0.007-0.086 mg/L (average, 0.041 mg/L) (Dabeka and McKenzie 1987). A sample of soy milk contained much more fluoride than a sample of dairy milk, with a measured concentration of 0.491 mg/L (Liu et al. 1995).

Infant formulas vary in fluoride content, depending on the type of formula and the water with which it is prepared. Dabeka and McKenzie (1987) reported mean fluoride concentrations in ready-to-use formulas of 0.23 mg/L for formulas manufactured in the United States and 0.90 mg/L for formulas manufactured in Canada. Van Winkle et al. (1995) analyzed 64 infant formulas, 47 milk-based and 17 soy-based. For milk-based formulas, mean fluoride concentrations were 0.17 mg/L for ready-to-feed, 0.12 mg/L for liquid concentrates reconstituted with distilled water, and 0.14 mg/L for powdered concentrates reconstituted with distilled water. Mean fluoride concentrations for soy-based formulas were 0.30, 0.24, and 0.24 mg/L for ready-to-feed, liquid concentrates, and powdered concentrates, respectively (the latter two were reconstituted with distilled water). Obviously, the fluoride concentration in home-prepared formula depends on the fluoride concentrations in both the formula concentrate and the home.
MEASURES OF EXPOSURE TO FLUORIDE IN THE UNITED STATES

drinking water. Fomon et al. (2000) have recommended using low-fluoride water to dilute infant formulas.

Heilman et al. (1997) found 0.01 to 8.38 µg of fluoride per g of prepared infant foods. The highest concentrations were found in chicken (1.05-8.38 µg/g); other meats varied from 0.01 µg/g (veal) to 0.66 µg/g (turkey). Other foods—fruits, desserts, vegetables, mixed foods, and cereals—ranged from 0.01 to 0.63 µg/g. The fluoride concentrations in most foods are attributable primarily to the water used in processing (Heilman et al. 1997); fluoride in chicken is due to processing methods (mechanical deboning) that leave skin and residual bone particles in the meat (Heilman et al. 1997; Fein and Cerklewski 2001). An infant consuming 2 oz (about 60 g) of chicken daily at 8 µg of fluoride per g would have an intake of about 0.48 mg (Heilman et al. 1997).

Tea can contain considerable amounts of fluoride, depending on the type of tea and its source. Tea plants take up fluoride from soil along with aluminum (Shu et al. 2003; Wong et al. 2003). Leaf tea, including black tea and green tea, is made from the buds and young leaves of the tea plant, the black tea with a fermentation process, and the green tea without. Oolong tea is intermediate between black and green tea. Brick tea, considered a low-quality tea, is made from old (mature) leaves and sometimes branches and fruits of the tea plant (Shu et al. 2003; Wong et al. 2003). Fluoride accumulates mostly in the leaves of the tea plant, especially the mature or fallen leaves. Measured fluoride concentrations in tea leaves range from 170 to 878 mg/kg in different types of tea, with brick tea generally having 2-4 times as much fluoride as leaf tea (Wong et al. 2003). Commercial tea brands in Sichuan Province of China ranged from 49 to 105 mg/kg dry weight for green teas and 590 to 708 mg/kg dry weight for brick teas (Shu et al. 2003). Infusions of Chinese leaf tea (15 kinds) made with distilled water have been shown to have fluoride at 0.6-1.9 mg/L (Wong et al. 2003). Brick teas, which are not common in the United States, contain 4.8-7.3 mg/L; consumption of brick teas has been associated with fluorosis in some countries (Wong et al. 2003).

Chan and Koh (1996) measured fluoride contents of 0.34-3.71 mg/L (mean, 1.50 mg/L) in caffeinated tea infusions (made with distilled, deionized water), 1.01-5.20 mg/L (mean, 3.19 mg/L) in decaffeinated tea infusions, and 0.02-0.15 mg/L (mean, 0.05 mg/L) in herbal tea infusions, based on 44 brands of tea available in the United States (Houston area). Whyte et al. (2005) reported fluoride concentrations of 1.0-6.5 mg/L in commercial teas (caffeinated and decaffeinated) obtained in St. Louis (prepared with distilled water according to label directions). Warren et al. (1996) found fluoride contents of 0.10-0.58 mg/L in various kinds and brands of coffee sold in the United States (Houston area), with a slightly lower mean for decaffeinated (0.14 mg/L) than for caffeinated (0.17 mg/L) coffee. Instant
fluoride in drinking water

Coffee had a mean fluoride content of 0.30 mg/L (all coffees tested were prepared with deionized distilled water). Fluoride concentrations of 0.03 mg/L (fruit tea) to 3.35 mg/L (black tea) were reported for iced-tea products sold in Germany primarily by international companies (Behrendt et al. 2002).

In practice, fluoride content in tea or coffee as consumed will be higher if the beverage is made with fluoridated water; however, for the present purposes, the contribution from water for beverages prepared at home is included in the estimated intakes from drinking water, discussed earlier. Those estimates did not include commercially available beverages such as fruit juices (not including water used to reconstitute frozen juices), juice-flavored drinks, iced-tea beverages, carbonated soft drinks, and alcoholic beverages. Kiritsy et al. (1996) reported fluoride concentrations in juices and juice-flavored drinks of 0.02-2.8 mg/L (mean, 0.56 mg/L) for 532 different drinks (including five teas) purchased in Iowa City (although many drinks represented national or international distribution); frozen-concentrated beverages were reconstituted with distilled water before analysis. White grape juices had the highest mean fluoride concentration (1.45 mg/L); upper limits on most kinds of juices exceeded 1.50 mg/L. Stannard et al. (1991) previously reported fluoride concentrations from 0.15 to 6.80 mg/L in a variety of juices originating from a number of locations in the United States. The variability in fluoride concentrations is due primarily to variability in fluoride concentrations in the water used in manufacturing the product (Kiritsy et al. 1996). The high fluoride content of grape juices (and grapes, raisins, and wines), even when little or no manufacturing water is involved, is thought to be due to a pesticide (cryolite) used in grape growing (Stannard et al. 1991; Kiritsy et al. 1996; Burgstahler and Robinson 1997).

Heilman et al. (1999) found fluoride concentrations from 0.02 to 1.28 mg/L (mean, 0.72 mg/L) in 332 carbonated beverages from 17 production sites, all purchased in Iowa. In general, these concentrations reflect that of the water used in manufacturing. Estimated mean intakes from the analyzed beverages were 0.36 mg/day for 2- to 3-year-old children and 0.60 mg/day for 7- to 10-year-olds (Heilman et al. 1999). Pang et al. (1992) estimated mean daily fluoride intakes from beverages (excluding milk and water) for children of 0.36, 0.54, and 0.60 mg, for ages 2-3, 4-6, and 7-10, respectively; daily total fluid intake ranged from 970 to 1,240 mL, and daily beverage consumption ranged from 585 to 756 mL.

Burgstahler and Robinson (1997) reported fluoride contents of 0.23-2.80 mg/L in California wines, with 7 of 19 samples testing above 1 mg/L; the fluoride in wine and in California grapes (0.83-5.20 mg/kg; mean, 2.71 mg/kg) was attributed to the use of cryolite (Na₃AlF₆) as a pesticide in the vineyards. Martínez et al. (1998) reported fluoride concentrations from 0.03 to 0.68 mg/L in wines from the Canary Islands; most fluoride concentrations in the wines were in the range of 0.10-0.35 mg/L. A maximum legal thresh-
old of 1 mg/L for the fluoride concentration in wine has been established by
the Office International de la Vigne et du Vin (OIV 1990; cited by Martínez
et al. 1998). Warnakulasuriya et al. (2002) reported mean fluoride concen-
trations of 0.08-0.71 mg/L in beers available in Great Britain; one Irish beer
contained fluoride at 1.12 mg/L. Examples of fluoride intakes that could be
expected in heavy drinkers (8-12 drinks per day) are given in Table 2-5.

R.D. Jackson et al. (2002) reported mean fluoride contents from 0.12
µg/g (fruits) to 0.49 µg/g (grain products) in a variety of noncooked, nonre-
constituted foods (excluding foods prepared with water). Fluoride contents
in commercial beverages (excluding reconstituted and fountain beverages)
averaged 0.55 µg/g; those in milk and milk products averaged 0.31 µg/g.
In the same study, fluoride contents in water, reconstituted beverages, and
cooked vegetables and grain products (cereals, pastas, soups) differed sig-
ificantly between two towns in Indiana, one with a water fluoride content
of 0.2 mg/L and one with an optimally fluoridated water supply (1.0 mg/L).
Bottled fruit drinks, water, and carbonated beverages purchased in the two
towns did not differ significantly. The mean daily fluoride ingestion for
children 3-5 years old from food and beverages (including those prepared
with community water) was estimated to be 0.454 mg in the low-fluoride
town and 0.536 mg in the fluoridated town.

Dabeka and McKenzie (1995) reported mean fluoride contents in vari-
ous food categories in Winnipeg, ranging up to 2.1 µg/g for fish, 0.61 µg/g
for soup, and 1.15 µg/g for beverages; the highest single items were cooked
veal (1.2 µg/g), canned fish (4.6 µg/g), shellfish (3.4 µg/g), cooked wheat
cereal (1.0 µg/g), and tea (5.0 µg/g). Estimated dietary intakes (including
fluoridated tap water) varied from 0.35 mg/day for children aged 1-4 to 3.0
mg/day for 40- to 64-year-old males. Over all ages and both sexes, the esti-

**TABLE 2-5** Examples of Fluoride Intakes by Heavy Drinkers from
Alcoholic Beverages Alone

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Fluoride Concentration, mg/L</th>
<th>Fluoride Intake, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 drinks per day</td>
</tr>
<tr>
<td>Beer (12-oz. cans or bottles)</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Wine (5-oz. glasses)</td>
<td>0.3</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Mixed drinks (1.5 oz. liquor + 6.5 oz. mixer and ice)</td>
<td>0.7a</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>1.0a</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*a*In carbonated soda and ice.
mated average dietary intake of fluoride was 1.76 mg/day; the food category contributing most to the estimated intake was beverages (80%).

Rojas-Sanchez et al. (1999) estimated fluoride intakes for children (aged 16-40 months) in three communities in Indiana, including a low-fluoride community, a “halo” community (not fluoridated, but in the distribution area of a fluoridated community), and a fluoridated community. For fluoride in food, the mean intakes were 0.116-0.146 mg/day, with no significant difference between communities. Intake from beverages was estimated to be 0.103, 0.257, and 0.396 mg/day for the low-, halo, and high-fluoride communities; differences between the towns were statistically significant.

Apart from drinking water (direct and indirect consumption, as described earlier), the most important foods in terms of potential contribution to individual fluoride exposures are infant formula, commercial beverages such as juice and soft drinks, grapes and grape products, teas, and processed chicken (Table 2-6). Grapes and grape products, teas, and processed chicken can be high in fluoride apart from any contribution from preparation or process water. Commercial beverages and infant formulas, however, greatly depend on the fluoride content of the water used in their preparation or manufacture (apart from water used in their in-home preparation); due to widespread distribution, such items could have similar fluoride concentrations in most communities, on average.

### TABLE 2-6 Summary of Typical Fluoride Concentrations of Selected Food and Beverages in the United States

<table>
<thead>
<tr>
<th>Source</th>
<th>Range, mg/L</th>
<th>Range, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human breast milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoridated area (1 mg/L)</td>
<td>0.007-0.01</td>
<td>—</td>
</tr>
<tr>
<td>Nonfluoridated area</td>
<td>0.004</td>
<td>—</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>≤0.07</td>
<td>—</td>
</tr>
<tr>
<td>Soy milk</td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>Milk-based infant formula(^a)</td>
<td>≤0.2</td>
<td>—</td>
</tr>
<tr>
<td>Soy-based infant formula(^a)</td>
<td>0.2-0.3</td>
<td>—</td>
</tr>
<tr>
<td>Infant food—chicken</td>
<td>—</td>
<td>1.8</td>
</tr>
<tr>
<td>Infant food—other</td>
<td>—</td>
<td>0.01-0.7</td>
</tr>
<tr>
<td>Tea(^a)</td>
<td>0.3-5</td>
<td>—</td>
</tr>
<tr>
<td>Herbal tea(^a)</td>
<td>0.02-0.15</td>
<td>—</td>
</tr>
<tr>
<td>Coffee(^a)</td>
<td>0.1-0.6</td>
<td>—</td>
</tr>
<tr>
<td>Grape juice(^a)</td>
<td>≤3</td>
<td>—</td>
</tr>
<tr>
<td>Other juices and juice drinks(^a)</td>
<td>≤1.5</td>
<td>—</td>
</tr>
<tr>
<td>Grapes</td>
<td>—</td>
<td>0.8-5</td>
</tr>
<tr>
<td>Carbonated beverages</td>
<td>0.02-1.3</td>
<td>—</td>
</tr>
<tr>
<td>Wine</td>
<td>0.2-3</td>
<td>—</td>
</tr>
<tr>
<td>Beer</td>
<td>0.08-1</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Not including contribution from local tap water.
Because of the wide variability in fluoride content in items such as tea, commercial beverages and juices, infant formula, and processed chicken, and the possibility of a substantial contribution to an individual's total fluoride intake, a number of authors have suggested that such fluoride sources be considered in evaluating an individual's need for fluoride supplementation (Clovis and Hargreaves 1988; Stannard et al. 1991; Chan and Koh 1996; Kiritsy et al. 1996; Warren et al. 1996; Heilman et al. 1997, 1999; Levy and Guha-Chowdhury 1999), especially for individuals who regularly consume large amounts of a single product (Stannard et al. 1991; Kiritsy et al. 1996). Several authors also point out the difficulty in evaluating individual fluoride intake, given the wide variability of fluoride content among similar items (depending on point of origin, etc.), the wide distribution of many products, and the lack of label or package information about fluoride content for most products (Stannard et al. 1991; Chan and Koh 1996; Behrendt et al. 2002).

Dental Products and Supplements

Fluoridated dental products include dentifrices (toothpastes, powders, liquids, and other preparations for cleaning teeth) for home use and various gels and other topical applications for use in dental offices. More than 90% of children ages 2-16 years surveyed in 1983 or 1986 used fluoride toothpaste (Wagener et al. 1992). Of these children, as many as 15% to 20% in some age groups also used fluoride supplements or mouth rinses (Wagener et al. 1992). Using the same 1986 survey data, Nourjah et al. (1994) reported that most children younger than 2 years of age used fluoride dentifrices.

Most toothpaste sold in the United States contains fluoride (Newbrun 1992), usually 1,000-1,100 parts per million (ppm) (0.1-0.11%). The amount of fluoride actually swallowed by an individual depends on the amount of toothpaste used, the swallowing control of the person (especially for young children), and the frequency of toothpaste use. Ophaug et al. (1980, 1985) estimated the intake of fluoride by small children (2-4 years) to be 0.125-0.3 mg per brushing; a 2-year-old child brushing twice daily would ingest nearly as much fluoride from the toothpaste as from food and fluoridated drinking water combined (Ophaug et al. 1985). Levy and Zarei-M (1991) reported estimates of 0.12-0.38 mg of fluoride ingested per brushing. Burt (1992) and Newbrun (1992) reported estimates of 0.27

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10Equivalent to 1-1.1 mg fluoride ion per gram of toothpaste. This may be expressed in various ways on the package, e.g., as 0.24% or 0.243% sodium fluoride (NaF), 0.76% or 0.8% monofluorophosphate (Na$_2$PO$_3$F), or 0.15% w/v fluoride (1.5 mg fluoride ion per cubic centimeter of toothpaste).
mg/day for a preschool child brushing twice daily with standard-strength (1,000 ppm) toothpaste.

Levy (1993, 1994) and Levy et al. (1995a) reviewed a number of studies of the amount of toothpaste people of various ages ingest. Amounts of toothpaste used per brushing range from 0.2 to 5 g, with means around 0.4-2 g, depending on the age of the person. The estimated mean percentage of toothpaste ingested ranges from 3% in adults to 65% in 2-year-olds. Children who did not rinse after toothbrushing ingested 75% more toothpaste than those who rinsed. Perhaps 20% of children have fluoride intakes from toothpaste several times greater than the mean values, and some children probably get more than the recommended amount of fluoride from toothpaste alone, apart from food and beverages (Levy 1993, 1994). Mean intakes of toothpaste by adults were measured at 0.04 g per brushing (0.04 mg of fluoride per brushing for toothpaste with 0.1% fluoride), with the 90th percentile at 0.12 g of toothpaste (0.12 mg of fluoride) per brushing (Barnhart et al. 1974).

Lewis and Limeback (1996) estimated the daily intake of fluoride from dentifrice (products for home use) to be 0.02-0.06, 0.008-0.02, 0.0025, and 0.001 mg/kg, for ages 7 months to 4 years, 5-11 years, 12-19 years, and 20+ years, respectively. Rojas-Sanchez et al. (1999) estimated fluoride intake from dentifrice at between 0.42 and 0.58 mg/day in children aged 16-40 months in three communities in Indiana. Children tend to use more toothpaste when provided special “children’s” toothpaste than when given adult toothpaste (Levy et al. 1992; Adair et al. 1997), and many children do not rinse or spit after brushing (Naccache et al. 1992; Adair et al. 1997).

Estimates of typical fluoride ingestion from toothpaste are given by age group in Table 2-7; these estimates are for typical rather than high or upper-bound intakes, and many individuals could have substantially higher intakes. A number of papers have suggested approaches to decreasing children’s intake of fluoride from toothpaste, including decreasing the fluoride content in

<table>
<thead>
<tr>
<th>Age Group, years</th>
<th>Fluoride Intake, mg/day</th>
<th>Age Group, years</th>
<th>Fluoride Intake, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt; 0.5 b</td>
<td>0</td>
<td>Youth 13-19</td>
<td>0.2</td>
</tr>
<tr>
<td>Infants 0.5-1</td>
<td>0.1</td>
<td>Adults 20-49</td>
<td>0.1</td>
</tr>
<tr>
<td>Children 1-2</td>
<td>0.15</td>
<td>Adults 50+</td>
<td>0.1</td>
</tr>
<tr>
<td>Children 3-5</td>
<td>0.25</td>
<td>Females 13-49 c</td>
<td>0.1</td>
</tr>
<tr>
<td>Children 6-12</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aBased on information reviewed by Levy et al. (1995a). Estimates assume two brushings per day with fluoride toothpaste (0.1% fluoride) and moderate rinsing.

bAssumes no brushing before 6 months of age.

cWomen of childbearing age.

Topical applications of fluoride in a professional setting can lead to ingestion of 1.3-31.2 mg (Levy and Zarei-M 1991). Substantial ingestion of fluoride also has been demonstrated from the use of fluoride mouth rinse and self-applied topical fluoride gel (Levy and Zarei-M 1991). Heath et al. (2001) reported that 0.3-6.1 mg of fluoride (5-29% of total applied) was ingested by young adults who used gels containing 0.62-62.5 mg of fluoride.

Levy et al. (2003a) found that two-thirds of children had at least one fluoride treatment by age 6 and that children with dental caries were more likely to have had such a treatment. Their explanation is that professional application of topical fluoride is used mostly for children with moderate to high risk for caries. In contrast, Eklund et al. (2000), in a survey of insurance claims for more than 15,000 Michigan children treated by 1,556 different dentists, found no association between the frequency of use of topical fluoride (professionally applied) and restorative care. Although these were largely low-risk children, for whom routine use of professionally applied fluoride is not recommended, two-thirds received topical fluoride at nearly every office visit. The authors recommended that the effectiveness of professionally applied topical fluoride products in modern clinical practice be evaluated.

Exposures from topical fluorides during professional treatment are unlikely to be significant contributors to chronic fluoride exposures because they are used only a few times per year. However, they could be important with respect to short-term or peak exposures.

Heath et al. (2001) found that retention of fluoride ion in saliva after the use of dentifrice (toothpaste, mouthrinse, or gel) was proportional to the quantity used, at least for young adults. They were concerned with maximizing the retention in saliva to maximize the topical benefit of the fluoride. Sjögren and Melin (2001) were also concerned about enhancing the retention of fluoride in saliva and recommend minimal rinsing after toothbrushing. However, fluoride in saliva eventually will be ingested, so enhancing the retention of fluoride in saliva after dentifrice use also enhances the ingestion of fluoride from the dentifrice.

Fluoride supplements (NaF tablets, drops, lozenges, and rinses) are intended for prescriptions for children in low-fluoride areas; dosages generally range from 0.25 to 1.0 mg of fluoride/day (Levy 1994; Warren and Levy
Appropriate dosages should be based on age, risk factors (e.g., high risk for caries), and ingestion of fluoride from other sources (Dillenberg et al. 1992; Jones and Berg 1992; Levy and Muchow 1992; Levy 1994; Warren and Levy 1999). Although compliance is often considered to be a problem, inappropriate use of fluoride supplements has also been identified as a risk factor for enamel fluorosis (Dillenberg et al. 1992; Levy and Muchow 1992; Levy 1994; Pendrys and Morse 1995; Warren and Levy 1999).

The dietary fluoride supplement schedule in the United States, as revised in 1994 by the American Dental Association, now calls for no supplements for children less than 6 months old and none for any child whose water contains at least 0.6 mg/L (Record et al. 2000; ADA 2005; Table 2-8). Further changes in recommendations for fluoride supplements have been suggested (Fomon and Ekstrand 1999; Newbrun 1999; Fomon et al. 2000), including dosages based on individual body weight rather than age (Adair 1999) and the use of lozenges to be sucked rather than tablets to be swallowed (Newbrun 1999), although others disagree (Moss 1999). The Canadian recommendations for fluoride supplementation include an algorithm for determining the appropriateness for a given child and then a schedule of doses; no supplementation is recommended for children whose water contains at least 0.3 mg/L or who are less than 6 months old (Limeback et al. 1998; Limeback 1999b).

Fluoride in Air

Fluoride (either as hydrogen fluoride, particulate fluorides, or fluorine gas) is released to the atmosphere by natural sources such as volcanoes and by a number of anthropogenic sources. In North America, anthropogenic sources of airborne fluoride include coal combustion by electrical utilities and other entities, aluminum production plants, phosphate fertilizer plants, chemical production facilities, steel mills, magnesium plants, and manufacturers of brick and structural clay (reviewed by ATSDR 2003). Estimated airborne releases of hydrogen fluoride in the United States in 2001 were 67.4 million pounds (30.6 million kg; TRI 2003), of which at least 80% was attributed to electrical utilities (ATSDR 2003). Airborne releases of fluorine gas totaled about 9,000 pounds or 4,100 kg (TRI 2003). Anthropogenic hydrogen fluoride emissions in Canada in the mid-1990s were estimated at 5,400 metric tons (5.4 million kg or 11.9 million pounds), of which 75% was attributed to primary aluminum producers (CEPA 1996).

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11Volcanic activity historically has been a major contributor of HF and other contaminants to the atmosphere in some parts of the world, with some volcanoes emitting 5 tons of HF per day (Nicaragua) or as much as 15 million tons during a several month eruption (Iceland) (Durand and Grattan 2001; Grattan et al. 2003; Stone 2004).
Measured fluoride concentrations in air in the United States and Canada typically range from 0.01 to 1.65 µg/m³, with most of it (75%) present as hydrogen fluoride (CEPA 1996). The highest concentrations (>1 µg/m³) correspond to urban locations or areas in the vicinity of industrial operations. Historically, concentrations ranging from 2.5 to 14,000 µg/m³ have been reported near industrial operations in various countries (reviewed by EPA 1988). Ernst et al. (1986) reported an average concentration of airborne fluoride of about 600 µg/m³ during the 1981 growing season in a rural inhabited area (Cornwall Island) on the U.S.-Canadian border directly downwind from an aluminum smelter. Hydrogen fluoride is listed as a hazardous air pollutant in the Clean Air Act Amendments of 1990 (reviewed by ATSDR 2003), and as such, its emissions are subject to control based on “maximum achievable control technology” emission standards. Such standards are already in effect for fluoride emissions from primary and secondary aluminum production, phosphoric acid manufacture and phosphate fertilizer production, and hydrogen fluoride production (ATSDR 2003).

For most individuals in the United States, exposure to airborne fluoride is expected to be low compared with ingested fluoride (EPA 1988); exceptions include people in heavily industrialized areas or having occupational exposure. Assuming inhalation rates of 10 m³/day for children and 20 m³/day for adults, fluoride exposures from inhalation in rural areas (<0.2 µg/m³ fluoride) would be less than 2 µg/day (0.0001-0.0002 mg/kg/day) for a child and 4 µg/day (0.00006 mg/kg/day) for an adult. In urban areas (<2 µg/m³), fluoride exposures would be less than 20 µg/day (0.0001-0.0002 mg/kg/day) for a child and 40 µg/day (0.0006 mg/kg/day) for an adult. Lewis and Limeback (1996) used an estimate of 0.01 µg/kg/day (0.00001 mg/kg/day) for inhaled fluoride for Canadians; this would equal 0.1 µg/day for a 10-kg child or 0.7 µg/day for a 70-kg adult.

Occupational exposure at the Occupational Safety and Health Administration (OSHA) exposure limit of 2.5 mg/m³ would result in a fluoride intake of 16.8 mg/day for an 8-hour working day (0.24 mg/kg/day for a

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**TABLE 2-8** Dietary Fluoride Supplement Schedule of 1994

<table>
<thead>
<tr>
<th>Age</th>
<th>Fluoride Concentration in Drinking Water, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.3</td>
</tr>
<tr>
<td>Birth to 6 months</td>
<td>None</td>
</tr>
<tr>
<td>6 months to 3 years</td>
<td>0.25 mg/day</td>
</tr>
<tr>
<td>3-6 years</td>
<td>0.50 mg/day</td>
</tr>
<tr>
<td>6-16 years</td>
<td>1.0 mg/day</td>
</tr>
</tbody>
</table>

70-kg person) (ATSDR 2003). Heavy cigarette smoking could contribute as much as 0.8 mg of fluoride per day to an individual (0.01 mg/kg/day for a 70-kg person) (EPA 1988).

Fluoride in Soil

Fluoride in soil could be a source of inadvertent ingestion exposure, primarily for children. Typical fluoride concentrations in soil in the United States range from very low (<10 ppm) to as high as 3% to 7% in areas with high concentrations of fluorine-containing minerals (reviewed by ATSDR 2003). Mean or typical concentrations in the United States are on the order of 300-430 ppm. Soil fluoride content may be higher in some areas due to use of fluoride-containing phosphate fertilizers or to deposition of airborne fluoride released from industrial operations.

Estimated values for inadvertent soil ingestion by children (excluding those with pica) are 100 mg/day (mean) and 400 mg/day (upper bound) (EPA 1997); the estimated mean value for soil ingestion by adults is 50 mg/day (EPA 1997). For a typical fluoride concentration in soil of 400 ppm, therefore, estimated intakes of fluoride by children would be 0.04 (mean) to 0.16 mg/day (upper bound) and by adults, 0.02 mg/day. For a 20-kg child, the mass-normalized intake would be 0.002-0.008 mg/kg/day; for a 70-kg adult, the corresponding value would be 0.0003 mg/kg/day. Erdal and Buchanan (2005) estimated intakes of 0.0025 and 0.01 mg/kg/day for children (3-5 years), for mean and reasonable maximum exposures, respectively, based on a fluoride concentration in soil of 430 ppm. In their estimates, fluoride intake from soil was 5-9 times lower than that from fluoridated drinking water.

For children with pica (a condition characterized by consumption of nonfood items such as dirt or clay), an estimated value for soil ingestion is 10 g/day (EPA 1997). For a 20-kg child with pica, the fluoride intake from soil containing fluoride at 400 ppm would be 4 mg/day or 0.2 mg/kg/day. Although pica in general is not uncommon among children, the prevalence is not known (EPA 1997). Pica behavior specifically with respect to soil or dirt appears to be relatively rare but is known to occur (EPA 1997); however, fluoride intake from soil for a child with pica could be a significant contributor to total fluoride intake. For most children and for adults, fluoride intake from soil probably would be important only in situations in which the soil fluoride content is high, whether naturally or due to industrial pollution.

Pesticides

Cryolite and sulfuryl fluoride are the two pesticides that are regulated for their contribution to the residue of inorganic fluoride in foods. For food
use pesticides, EPA establishes a tolerance for each commodity to which a pesticide is allowed to be applied. Tolerance is the maximum amount of pesticide allowed to be present in or on foods. In the environment, cryolite breaks down to fluoride, which is the basis for the safety evaluation of cryolite and synthetic cryolite pesticides (EPA 1996a). Fluoride ions are also degradation products of sulfuryl fluoride (EPA 1992). Thus, the recent evaluation of the dietary risk of sulfuryl fluoride use on food takes into account the additional exposure to fluoride from cryolite (EPA 2004). Sulfuryl fluoride is also regulated as a compound with its own toxicologic characteristics.

Cryolite, sodium hexafluoroaluminate (Na$_3$AlF$_6$), is a broad spectrum insecticide that has been registered for use in the United States since 1957. Currently, it is used on many food (tree fruits, berries, and vegetables) and feed crops, and on nonfood ornamental plants (EPA 1996a). The respective fluoride ion concentrations from a 200 ppm aqueous synthetic cryolite (97.3% pure) at pH 5, 7, and 9 are estimated at 16.8, 40.0, and 47.0 ppm (approximately 15.5%, 37%, and 43% of the total available fluorine) (EPA 1996a). A list of tolerances for the insecticidal fluorine compounds cryolite and synthetic cryolite is published in the Code of Federal Regulations (40 CFR § 180.145(a, b, c) [2004]). Current tolerances for all commodities are at 7 ppm.

Sulfuryl fluoride (SO$_2$F$_2$), is a structural fumigant registered for use in the United States since 1959 for the control of insects and vertebrate pests. As of January 2004, EPA published a list of tolerances for sulfuryl fluoride use as a post-harvest fumigant for grains, field corn, nuts, and dried fruits (69 Fed. Reg. 3240 [2004]; 40 CFR 180.575(a) [2004]). The calculated exposure threshold at the drinking-water MCL of 4 mg/L was used as the basis for assessing the human health risk associated with these decisions (EPA 2004).

Concerns were raised that foods stored in the freezer during sulfuryl fluoride residential fumigation might retain significant amounts of fluoride residue. Scheffrahn et al. (1989) reported that unsealed freezer foods contained fluoride at as high as 89.7 ppm (flour, at 6,803 mg-hour/L rate of sulfuryl fluoride application) while no fluoride residue was detected (0.8 ppm limit of detection) in foods that were sealed with polyethylene film. A later study reported fluoride residue above 1 ppm in food with higher fat contents (e.g., 5.643 ppm in margarine) or that was improperly sealed (e.g., 7.66 ppm in a reclosed peanut butter PETE [polyethylene terephthalate] jar) (Scheffrahn et al. 1992).

Dietary exposure for a food item is calculated as the product of its consumption multiplied by the concentration of the residue of concern. The total daily dietary exposure for an individual is the sum of exposure from all food items consumed in a day. A chronic dietary exposure assessment of
Fluoride was recently conducted for supporting the establishment of tolerances for the post-harvest use of sulfuryl fluoride. EPA (2004) used the Dietary Exposure Evaluation Model (DEEM-FCID), a computation program, to estimate the inorganic fluoride exposure from cryolite, sulfuryl fluoride, and the background concentration of fluoride in foods. DEEM-FCID (Exponent, Inc) uses the food consumption data from the 1994-1996 and 1998 Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the U.S. Department of Agriculture (USDA). The 1994-1996 database consists of food intake diaries of more than 15,000 individuals nationwide on two nonconsecutive days. A total of 4,253 children from birth to 9 years of age are included in the survey. To ensure that the eating pattern of young children is adequately represented in the database, an additional survey was conducted in 1998 of 5,559 children 0-9 years of age. The latter survey was designed to be compatible with the CSFII 1994-1996 data so that the two sets of data can be pooled to increase the sample size for children. The Food Commodity Intake Database (FCID) is jointly developed by EPA and USDA for the purpose of estimating dietary exposure from pesticide residues in foods. It is a translated version of the CSFII data that expresses the intake of consumed foods in terms of food commodities (e.g., translating apple pie into its ingredients, such as apples, flour, sugar, etc.) (EPA 2000c).

All foods and food forms (e.g., grapes—fresh, cooked, juice, canned, raisins, wine) with existing tolerances for cryolite and sulfuryl fluoride were included in the recent EPA fluoride dietary exposure analysis (EPA 2004). For the analysis of fluoride exposure from cryolite, residue data taken from monitoring surveys, field studies, and at tolerance were adjusted to reflect changes in concentration during food processing (e.g., mixing in milling, dehydration, and food preparation). For the fluoride exposure from post-harvest treatment with sulfuryl fluoride, the measured residues are used without further adjustment except for applying drawdown factors in grain mixing (EPA 2004). In estimating fluoride exposure from both cryolite- and sulfuryl fluoride-treated foods, residue concentrations were adjusted for the percentage of crop treated with these pesticides based on the information from market share and agricultural statistics on pesticide use.

Fluoride exposures from a total of 543 forms of foods (e.g., plant-based, bovine, poultry, egg, tea) containing fluoride were also estimated as the background food exposure. Residue data were taken from surveys and residue trials (EPA 2004). No adjustments were made to account for residue concentration through processing or dehydration. Theoretically, the exposure from some processed foods (e.g., dried fruits) could potentially be higher than if their residue concentrations were assumed to be the same as in the fresh commodities (e.g., higher exposure from higher residue in dried fruits than assuming same residue concentration for both dried and fresh fruits.) However, these considerations are apparently offset by the
use of higher residue concentrations for many commodities (e.g., using the highest values from a range of survey data, the highest value as surrogate for when data are not available, assuming residue in dried fruits and tree nuts at one-half the limit of quantification when residue is not detected) such that the overall dietary exposure was considered overestimated (EPA 2004). The dietary fluoride exposure thus estimated ranged from 0.0003 to 0.0031 mg/kg/day from cryolite, 0.0003 to 0.0013 mg/kg/day from sulfuryl fluoride, and 0.005 to 0.0175 mg/kg/day from background concentration in foods (EPA 2004). Fine-tuning the dietary exposure analysis using the comprehensive National Fluoride Database recently published by USDA (2004) for many foods also indicates that the total background food exposure would not be significantly different from the analysis by EPA, except for the fluoride intake from tea. A closer examination of the residue profile used by EPA (2004) for background food exposure analysis reveals that 5 ppm, presumably a high-end fluoride concentration in brewed tea, was entered in the residue profile that called for fluoride concentration in powdered or dried tea. According to the USDA survey database (2004), the highest detected fluoride residue in instant tea powder is 898.72 ppm. The corrected exposure estimate is presented in the section “Total Exposure to Fluoride” later in this chapter.

Fluorinated Organic Chemicals

Many pharmaceuticals, consumer products, and pesticides contain organic fluorine (e.g., –CF₃, –SCF₃, –OCF₃). Unlike chlorine, bromine, and iodine, organic fluorine is not as easily displaced from the alkyl carbon and is much more lipophilic than the hydrogen substitutes (Daniels and Jorgensen 1977; PHS 1991). The lipophilic nature of the trifluoromethyl group contribute to the enhanced biological activity of some pharmaceutical chemicals.

The toxicity of fluorinated organic chemicals usually is related to their molecular characteristics rather than to the fluoride ions metabolically displaced. Fluorinated organic chemicals go through various degrees of biotransformation before elimination. The metabolic transformation is minimal for some chemicals. For example, the urinary excretion of ciprofloxacin (fluoroquinolone antibacterial agent) consists mainly of the unchanged parent compound or its fluorine-containing metabolites (desethylene-, sulfo-, oxo-, and N-formyl ciprofloxacin) (Bergan 1989). Nevertheless, Pradhan et al. (1995) reported an increased serum fluoride concentration from 4 µM (0.076 ppm) to 11 µM (0.21 ppm) in 19 children from India (8 months to 13 years old) within 12 hours after the initial oral dose of ciprofloxacin at 15-25 mg/kg. The presumed steady state (day 7 of repeated dosing) 24-hour urinary fluoride concentration was 15.5% higher than the predosing...
concentration (59 μM versus 51 μM; or, 1.12 ppm versus 0.97 ppm). Another example of limited contribution to serum fluoride concentration from pharmaceuticals was reported for flecainide, an antiarrhythmic drug. The peak serum fluoride concentration ranged from 0.0248 to 0.0517 ppm (1.3 to 2.7 μM) in six healthy subjects (26-54 years old, three males, and three females) 4.5 hours after receiving a single oral dose of 100 mg of flecainide acetate (Rimoli et al. 1991). One to two weeks before the study, the subjects were given a poor fluoride diet, used toothpaste without fluoride, and had low fluoride (0.08 mg/L) in their drinking water.

Other fluoride-containing organic chemicals go through more extensive metabolism that results in greater increased bioavailability of fluoride ion. Elevated serum fluoride concentrations from fluorinated anesthetics have been extensively studied because of the potential nephrotoxicity of methoxyflurane in association with elevated serum fluoride concentrations beyond a presumed toxicity benchmark of 50 μM (Cousins and Mazze 1973; Mazze et al. 1977). A collection of data on peak serum fluoride ion concentrations from exposures to halothane, enflurane, isoflurane, and sevoflurane is given in Appendix B. These data serve to illustrate a wide range of peak concentrations associated with various use conditions (e.g., length of use, minimum alveolar concentration per hour), biological variations (e.g., age, gender, obesity, smoking), and chemical-specific characteristics (e.g., biotransformation pattern and rates). It is not clear how these episodically elevated serum fluoride ion concentrations contribute to potential adverse effects of long-term sustained exposure to inorganic fluoride from other media, such as drinking water, foods, and dental-care products.

Elevated free fluoride ion (< 2% of administered dose) also was detected in the plasma and urine of some patients after intravenous administration of fluorouracil (Hull et al. 1988). Nevertheless, the major forms of urinary excretion were still the unchanged parent compound and its fluorine-containing metabolites (dihydrofluorouracil, α-fluoro-β-ureidopropanoic acid, α-fluoro-β-alanine). The extent of dermal absorption of topical fluorouracil cream varies with skin condition, product formulation, and the conditions of use. Levy et al. (2001a) reported less than 3% systemic fluorouracil absorption in patients treated with 0.5% or 5% cream for actinic keratosis.

A group of widely used consumer products is the fluorinated telomers and polytetrafluoroethylene, or Teflon. EPA is in the process of evaluating the environmental exposure to low concentrations of perfluorooctanoic acid (PFOA) and its principal salts that are used in manufacturing fluoropolymers or as their breakdown products (EPA 2003b). PFOA is persistent in the environment. It is readily absorbed through oral and inhalation exposure and is eliminated in urine and feces without apparent biotransformation (EPA 2003b; Kudo and Kawashima 2003). Unchanged plasma and urine fluoride concentrations in rats that received intraperitoneal injections of
PFOA also indicated a lack of defluorination (Vanden Heuvel et al. 1991). (See Chapter 3 for more discussion of PFOA.)

Aluminofluorides, Beryllofluorides, and Fluorosilicates

Aluminofluorides and Beryllofluorides

Complexes of aluminum and fluoride (aluminofluorides, most often AlF$_3$ or AlF$_4^-$) or beryllium and fluoride (beryllofluorides, usually as BeF$_3^-$) occur when the two elements are present in the same environment (Struneczka and Patocka 2002). Fluoroaluminate complexes are the most common forms in which fluoride can enter the environment. Eight percent of the earth’s crust is composed of aluminum; it is the most abundant metal and the third most abundant element on earth (Liptrot 1974). The most common form for the inorganic salt of aluminum and fluoride is cryolite (Na$_3$AlF$_6$). In fact, of the more than 60 metals on the periodic chart, Al$^{3+}$ binds fluoride most strongly (Martin 1988). With the increasing prevalence of acid rain, metal ions such as aluminum become more soluble and enter our day-to-day environment; the opportunity for bioactive forms of AlF to exist has increased in the past 100 years. Human exposure to aluminofluorides can occur when a person ingests both a fluoride source (e.g., fluoride in drinking water) and an aluminum source; sources of human exposure to aluminum include drinking water, tea, food residues, infant formula, aluminum-containing antacids or medications, deodorants, cosmetics, and glassware (ATSDR 1999; Struneczka and Patocka 2002; Li 2003; Shu et al. 2003; Wong et al. 2003). Aluminum in drinking water comes both from the alum used as a coagulant in water treatment and from leaching of aluminum into natural water by acid rain (ATSDR 1999; Li 2003). Exposure specifically to aluminofluoride complexes is not the issue so much as the fact that humans are routinely exposed to both elements. Human exposure to beryllium occurs primarily in occupational settings, in the vicinity of industrial operations that process or use beryllium, and near sites of beryllium disposal (ATSDR 2002).

Aluminofluoride and beryllofluoride complexes appear to act as analogues of phosphate groups—for example, the terminal phosphate of guanidine triphosphate (GTP) or adenosine triphosphate (ATP) (Chabre 1990; Antonny and Chabre 1992; Caverzasio et al. 1998; Façanha and Okorokova-Façanha 2002; Struneczka and Patocka 2002; Li 2003). Thus, aluminofluorides might influence the activity of a variety of phosphatases, phosphorylases, and kinases, as well as the G proteins involved in biological signaling systems, by inappropriately stimulating or inhibiting normal function of the protein (Yatani and Brown 1991; Caverzasio et al. 1998; Façanha and Okorokova-Façanha 2002; Struneczka and Patocka 2002; Li 2003).
Aluminofluoride complexes have been reported to increase the concentrations of second messenger molecules (e.g., free cytosolic Ca\(^{2+}\), inositol 1,4,5-trisphosphate, and cyclic AMP) for many bodily systems (Sternweis and Gilman 1982; Strunecka et al. 2002; Li 2003). The increased toxicity of beryllium in the presence of fluoride and vice versa was noted as early as 1949 (Stokinger et al. 1949). For further discussion of aluminofluorides, see Chapters 5 and 7.

Further research should include characterization of both the exposure conditions and the physiological conditions (for fluoride and for aluminum or beryllium) under which aluminofluoride and beryllofluoride complexes can be expected to occur in humans as well as the biological effects that could result.

**Fluorosilicates**

Most fluoride in drinking water is added in the form of fluosilicic acid (fluorosilicic acid, H\(_2\)SiF\(_6\)) or the sodium salt (sodium fluosilicate, Na\(_2\)SiF\(_6\)), collectively referred to as fluorosilicates (CDC 1993). Of approximately 10,000 fluoridated water systems included in the CDC’s 1992 fluoridation census, 75% of them (accounting for 90% of the people served) used fluorosilicates. This widespread use of silicofluorides has raised concerns on at least two levels. First, some authors have reported an association between the use of silicofluorides in community water and elevated blood concentrations of lead in children (Masters and Coplan 1999; Masters et al. 2000); this association is attributed to increased uptake of lead (from whatever source) due to incompletely dissociated silicofluorides remaining in the drinking water (Masters and Coplan 1999; Masters et al. 2000) or to increased leaching of lead into drinking water in systems that use chloramines (instead of chlorine as a disinfectant) and silicofluorides (Allegood 2005; Clabby 2005; Maas et al. 2005).\(^{12,13}\) Macek et al. (2006) have also compared blood lead concentrations in children by method of water fluoridation; they stated that their analysis did not support an association between blood lead concentrations and silicofluorides, but also could not refute it,  

\(^{12}\) In common practice, chloramines are produced with an excess of ammonia, which appears to react with silicofluorides to produce an ammonium-fluorosilicate intermediate which facilitates lead dissolution from plumbing components (Maas et al. 2005).

\(^{13}\) Another possible explanation for increased blood lead concentrations which has not been examined is the effect of fluoride intake on calcium metabolism; a review by Goyer (1995) indicates that higher blood and tissue concentrations of lead occur when the diet is low in calcium. Increased fluoride exposure appears to increase the dietary requirement for calcium (see Chapter 8); in addition, the substitution of tap-water based beverages (e.g., soft drinks or reconstituted juices) for dairy products would result in both increased fluoride intake and decreased calcium intake.
especially for children living in older housing. Second, essentially no studies have compared the toxicity of silicofluorides with that of sodium fluoride, based on the assumption that the silicofluorides will have dissociated to free fluoride before consumption (see also Chapter 7).

Use of more sophisticated analytical techniques such as nuclear magnetic resonance has failed to detect any silicon- and fluorine-containing species other than hexafluorosilicate ion (SiF$_{6}^{2-}$) (Urbansky 2002; Morris 2004). In drinking water at approximately neutral pH and typical fluoride concentrations, all the silicofluoride appears to be dissociated entirely to silicic acid [Si(OH)$_4$], fluoride ion, and HF (Urbansky 2002; Morris 2004); any intermediate species either exist at extremely low concentrations or are highly transient. SiF$_{6}^{2-}$ would be present only under conditions of low pH (pH < 5; Urbansky 2002; Morris 2004) and high fluoride concentration (above 16 mg/L according to Urbansky [2002]; at least 1 g/L to reach detectable levels of SiF$_{6}^{2-}$, according to Morris [2004]). Urbansky (2002) also stated that the silica contribution from the fluoridating agent is usually trivial compared with native silica in the water; therefore, addition of any fluoridating agent (or the presence of natural fluoride) could result in the presence of SiF$_{6}^{2-}$ in any water if other conditions (low pH and high total fluoride concentration) are met. Both Urbansky (2002) and Morris (2004) indicate that other substances in the water, especially metal cations, might form complexes with fluoride, which, depending on pH and other factors, could influence the amount of fluoride actually present as free fluoride ion. For example, P.J. Jackson et al. (2002) have calculated that at pH 7, in the presence of aluminum, 97.46% of a total fluoride concentration of 1 mg/L is present as fluoride ion, but at pH 6, only 21.35% of the total fluoride is present as fluoride ion, the rest being present in various aluminum fluoride species (primarily AlF$_2^{+}$ and AlF$_3$). Calculations were not reported for pH < 6.

Further research should include analysis of the concentrations of fluoride and various fluoride species or complexes present in tap water, using a range of water samples (e.g., of different hardness and mineral content). In addition, given the expected presence of fluoride ion (from any fluoridation source) and silica (native to the water) in any fluoridated tap water, it would be useful to examine what happens when that tap water is used to make acidic beverages or products (commercially or in homes), especially fruit juice from concentrate, tea, and soft drinks. Although neither Urbansky (2002) nor Morris (2004) discusses such beverages, both indicate that at pH < 5, SiF$_{6}^{2-}$ would be present, so it seems reasonable to expect that some SiF$_{6}^{2-}$ would be present in acidic beverages but not in the tap water used to prepare the beverages. Consumption rates of these beverages are high for many people, and therefore the possibility of biological effects of SiF$_{6}^{2-}$, as opposed to free fluoride ion, should be examined.
RECENT ESTIMATES OF TOTAL FLUORIDE EXPOSURE

A number of authors have reviewed fluoride intake from water, food and beverages, and dental products, especially for children (NRC 1993; Levy 1994; Levy et al. 1995a,b,c; Lewis and Limeback 1996; Levy et al. 2001b). Heller et al. (1999, 2000) estimated that a typical infant less than 1 year old who drinks fluoridated water containing fluoride at 1 mg/L would ingest approximately 0.08 mg/kg/day from water alone. Shulman et al. (1995) also calculated fluoride intake from water, obtaining an estimate of 0.08 mg/kg/day for infants (7-9 months of age), with a linearly declining intake with age to 0.034 mg/kg/day for ages 12.5-13 years.

Levy et al. (1995b,c; 2001b) have estimated the intake of fluoride by infants and children at various ages based on questionnaires completed by the parents in a longitudinal study. For water from all sources (direct, mixed with formula, etc.), the intake of fluoride by infants (Levy et al. 1995b) ranged from 0 (all ages examined) to as high as 1.73 mg/day (9 months old). Infants fed formula prepared from powdered or liquid concentrate had fluoride intakes just from water in the formula of up to 1.57 mg/day. The sample included 124 infants at 6 weeks old and 77 by 9 months old. Thirty-two percent of the infants at 6 weeks and 23% at age 3 months reportedly had no water consumption (being fed either breast milk or ready-to-feed formula without added water). Mean fluoride intakes for the various age groups ranged from 0.29 to 0.38 mg/day; however, these values include the children who consumed no water, and so are not necessarily applicable for other populations. For the same children, mean fluoride intakes from water, fluoride supplement (if used), and dentifrice (if used) ranged from 0.32 to 0.38 mg/day (Levy et al. 1995c); the maximum fluoride intakes ranged from 1.24 (6 weeks old) to 1.73 mg/day (9 months old). Ten percent of the infants at 3 months old exceeded an intake of 1.06 mg/day.

For a larger group of children (about 12,000 at 3 months and 500 by 36 months of age; Levy et al. 2001b), mean fluoride intakes from water, supplements, and dentifrice combined ranged from 0.360 mg/day (12 months old) to 0.634 mg/day (36 months old). The 90th percentiles ranged from 0.775 mg/day (16 months old) to 1.180 mg/day (32 months old). Maximum intakes ranged from 1.894 mg/day (16 months old) to 7.904 mg/day (9 months old) and were attributable only to water (consumption of well water with 5-6 mg/L fluoride; about 1% of the children had water sources containing more than 2 mg/L fluoride). For ages 1.5-9 months, approximately 40% of the infants exceeded a mass-normalized intake level for fluoride of 0.07 mg/kg/day; for ages 12-36 months, about 10-17% exceeded that level (Levy et al. 2001b).

Levy et al. (2003b) reported substantial variation in total fluoride intake among children aged 36-72 months, with some individual intakes greatly...
exceeding the means. The mean intake per unit of body weight declined with age from 0.05 to 0.06 mg/kg/day at 36 months to 0.03-0.04 mg/kg/day at 72 months; 90th percentile values declined from about 0.10 mg/kg/day to about 0.06 mg/kg/day (Levy et al. 2003b). Singer et al. (1985) reported mean estimated total fluoride intakes of 1.85 mg/day for 15- to 19-year-old males (based on a market-basket survey and a diet of 2,800 calories per day) in a fluoridated area (>0.7 mg/L) and 0.86 mg/day in nonfluoridated areas (<0.3 mg/L). Beverages and drinking water contributed approximately 75% of the total fluoride intake.

Lewis and Limeback (1996) estimated total daily fluoride intakes of 0.014-0.093 mg/kg for formula-fed infants and 0.0005-0.0026 mg/kg for breast-fed infants (up to 6 months). For children aged 7 months to 4 years, the estimated daily intakes from food, water, and household products (primarily dentifrice) were 0.087-0.160 mg/kg in fluoridated areas and 0.045-0.096 mg/kg in nonfluoridated areas. Daily intakes for other age groups were 0.049-0.079, 0.033-0.045, and 0.047-0.058 mg/kg for ages 5-11, 12-19, and 20+ in fluoridated areas, and 0.026-0.044, 0.017-0.021, and 0.032-0.036 mg/kg for the same age groups in nonfluoridated areas.

Rojas-Sanchez et al. (1999) estimated mean total daily fluoride intakes from foods, beverages, and dentifrice by 16- to 40-month-old children to be 0.767 mg (0.056 mg/kg) in a nonfluoridated community and 0.965 mg (0.070-0.073 mg/kg) in both a fluoridated community and a “halo” community. The higher mean dentifrice intake in the halo community than in the fluoridated community compensated for the lower dietary intake of fluoride in the halo community. Between 45% and 57% of children in the communities with higher daily fluoride intake exceeded the “upper estimated threshold limit” of 0.07 mg/kg, even without including any fluoride intake from supplements, mouth rinses, or gels in the study.

Erdal and Buchanan (2005), using a risk assessment approach based on EPA practices, estimated the cumulative (all sources combined) daily fluoride intake by infants (<1-year-old) in fluoridated areas to be 0.11 and 0.20 mg/kg for “central tendency” and “reasonable maximum exposure” conditions, respectively. For infants in nonfluoridated areas, the corresponding intakes were 0.08 and 0.11 mg/kg. For children aged 3-5, the estimated intakes were 0.06 and 0.23 mg/kg in fluoridated areas and 0.06 and 0.21 in nonfluoridated areas.

**TOTAL EXPOSURE TO FLUORIDE**

A systematic estimation of fluoride exposure from pesticides, background food, air, toothpaste, fluoride supplement, and drinking water is presented in this section. The estimated typical or average chronic exposures to inorganic fluoride from nonwater sources are presented in Table 2-9.
The exposures from pesticides (sulfuryl fluoride and cryolite), background food, and air are from a recent exposure assessment by EPA (2004). The background food exposure is corrected for the contribution from powdered or dried tea by using the appropriate residue concentration of 897.72 ppm.
for instant tea powder instead of the 5 ppm for brewed tea used in the EPA (2004) analysis. It should be noted that the exposure from foods treated with sulfuryl fluoride is not applicable before its registration for post-harvest fumigation in 2004. The exposure from toothpaste is based on Levy et al. (1995a; see Table 2-7). The use of fluoride-containing toothpaste is assumed not to occur during the first year of life. Fluoride supplements are considered separately in Table 2-9 and are not included in the “total nonwater” column. Children 1-2 years old have the highest exposures from all nonwater source components. The two highest nonwater exposure groups are children 1-2 and 3-5 years old, at 0.0389 and 0.0339 mg/kg/day, respectively (Table 2-9). These doses are approximately 2.5-3 times those of adult exposures.

The estimated exposures from drinking water are presented in Table 2-10, using the DEEM-FCID model (version 2.03, Exponent Inc.). The water consumption data are based on the FCID translated from the CSFII 1994-1996 and 1998 surveys and represent an update to the information presented in Appendix B. The food forms for water coded as “direct, tap”; “direct, source nonspecified”; “indirect, tap”; and “indirect, source nonspecified” are assumed to be from local tap water sources. The sum of these four categories constitutes 66-77% of the total daily water intake. The remaining 23-34% is designated as nontap, which includes four food forms coded as “direct, bottled”; “direct, others”; “indirect, bottled”; and

<table>
<thead>
<tr>
<th>TABLE 2-10 Estimated Chronic (Average) Inorganic Fluoride Exposure (mg/kg/day) from Drinking Water (All Sources)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Subgroups</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
</tr>
<tr>
<td>Nursing</td>
</tr>
<tr>
<td>Nonnursing</td>
</tr>
<tr>
<td>Children 1-2 years</td>
</tr>
<tr>
<td>Children 3-5 years</td>
</tr>
<tr>
<td>Children 6-12 years</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
</tr>
<tr>
<td>Adults 50+ years</td>
</tr>
<tr>
<td>Females 13-49 yearsb</td>
</tr>
</tbody>
</table>

*Estimated from DEEM-FCID model (version 2.03, Exponent Inc.). The water consumption data are based on diaries from the CSFII 1994-1996 and 1998 surveys that are transformed into food forms by the Food Commodity Intake Database (FCID). The food forms coded as “direct, tap”; “direct, source nonspecified”; “indirect, tap”; and “indirect, source nonspecified” are assumed to be from tap water sources.

bWomen of childbearing age.
Fluoride in Drinking Water: A Scientific Review of EPA's Standards

Fluoride exposures from drinking water (Table 2-10) are estimated for different concentrations of fluoride in the local tap water (0, 0.5, 1.0, 2.0, or 4.0 mg/L), while assuming a fixed 0.5 mg/L for all nontap sources (e.g., bottled water). The assumption for nontap water concentration is based on the most recent 6-year national public water system compliance monitoring from a 16-state cross section that represents approximately 41,000 public water systems, showing average fluoride concentrations of 0.482 mg/L in groundwater and 0.506 mg/L in surface water (EPA 2003a). The reported best estimates for exceeding 1.2, 2, and 4 mg/L in surface-water source systems are 9.37%, 1.11%, and 0.0491%, respectively; for groundwater source systems, the respective estimates are 8.54%, 3.05%, and 0.55%. Table 2-10 shows that nonnursing infants have the highest exposure from drinking water. The estimated daily drinking-water exposures at tap-water concentrations of 1, 2, and 4 mg/L are 0.0714, 0.129, and 0.243 mg/kg, respectively. These values are approximately 2.6 times those for children 1-2 and 3-5 years old and 4 times the exposure of adults.

The estimated total fluoride exposures aggregated from all sources are presented in Table 2-11. These values represent the sum of exposures from Table 2-9 and 2-10, assuming fluoride supplements might be given to infants and children up to 19 years old in low-fluoride tap-water scenarios (0 and 0.5 mg/L). Table 2-11 shows that, when tap water contains fluoride, nonnursing infants have the highest total exposure. They are 0.087, 0.144, and 0.258 mg/kg/day in tap water at 1, 2, and 4 mg/L, respectively. At 4 mg/L, the total exposure for nonnursing infants is approximately twice the exposure for children 1-2 and 3-5 years old and 3.4 times the exposure for adults.

The relative source contributions to the total exposure in Table 2-11 for scenarios with 1, 2, and 4 mg/L in tap water are illustrated in Figures 2-1, 2-2, and 2-3, respectively. Numerical values for the 1-, 2-, and 4-mg/L scenarios are given later in the summary tables (Tables 2-13, 2-14, and 2-15). Under the assumptions for estimating the exposure, the contribution from pesticides plus fluoride in the air is within 4% to 10% for all population subgroups at 1 mg/L in tap water, 3-7% at 2 mg/L in tap water, and 1-5% at 4 mg/L in tap water. The contributions from the remaining sources also vary with different tap-water concentrations. For nonnursing infants, who represent the highest total exposure group even without any exposure from toothpaste, the contribution from drinking water is 83% for 1 mg/L in tap water (Figure 2-1). As the tap-water concentration increases to 2 and 4 mg/L, the relative drinking-water contribution increases to 90% and 94%, respectively (Figures 2-2 and 2-3). The proportion of the contribution from all sources also varies in children 1-2 and 3-5 years old. At 1 mg/L, the drinking-water contribution is approximately 42%, while the contributions from toothpaste and background food are sizable, approximately 18% and
### TABLE 2-11 Total Estimated (Average) Chronic Inorganic Fluoride Exposure (mg/kg/day) from All Sources, Assuming Nontap Water at a Fixed Concentration

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Concentration in Tap Water (fixed nontap water at 0.5 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Fluoride Supplement</td>
</tr>
<tr>
<td></td>
<td>0 mg/L</td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.061</td>
</tr>
<tr>
<td>Nursing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.049</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.065</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.062</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>0.060</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>0.049</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
<td>0.033</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.017</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>0.015</td>
</tr>
<tr>
<td>Females 13-49 years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.016</td>
</tr>
</tbody>
</table>

<sup>a</sup>The estimated exposures from fluoride supplements and total nonwater sources (including pesticides, background food, air, and toothpaste) are from Table 2-9. The estimated exposures from drinking water are from Table 2-10. For nonfluoridated areas (tap water at 0 and 0.5 mg/L), the total exposures are calculated both with and without fluoride supplements.

<sup>b</sup>The higher total nonwater exposure of 0.0086 mg/kg/day that includes breast milk from a fluoridated area (footnote in Table 2-9) is used to calculate the exposure estimates for the “without supplement” groups that are exposed to fluoride in water at 1, 2, and 4 mg/L.

<sup>c</sup>Women of childbearing age.

31%, respectively (Figure 2-1). At 2 mg/L, the drinking-water contribution is raised to approximately 57%, while the contributions from toothpaste and background food are reduced to 13% and 23%, respectively (Figure 2-2). At 4 mg/L, the relative contribution of drinking water continues to increase to approximately 72%, while the contribution from toothpaste and background food are further reduced to approximately 9% and 15%, respectively (Figure 2-3). As age increases toward adulthood (20+ years), the contribution from toothpaste is reduced to approximately 5% at 1 mg/L, 3-4% at 2 mg/L, and 2% at 4 mg/L. Correspondingly, the contribution from drinking water increases to approximately 57% at 1 mg/L, 70% at 2 mg/L, and 82% at 4 mg/L.

Data presented in Tables 2-9 to 2-11 are estimates of typical exposures, while the actual exposure for an individual could be lower or higher. There are inherent uncertainties in estimating chronic exposure based on the 2-day CSFII surveys. The DEEM-FCID model assumes that the average
FIGURE 2-1 Source contribution to total inorganic fluoride exposure, including fluoride at 1 mg/L in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures as presented in Table 2-11 for the population subgroups are: 0.030 mg/kg/day (nursing infants), 0.087 mg/kg/day (non-nursing infants), 0.066 mg/kg/day (1-2 years old), 0.060 mg/kg/day (3-5 years old), 0.040 mg/kg/day (6-12 years old), 0.028 mg/kg/day (13-19 years old), and 0.031 mg/kg/day for adults (20 to 50+ years old) and women of childbearing age (13-49 years old).

intake from the cross-sectional survey represents the longitudinal average for a given population. Thus, the chronic exposures of those who have persistently high intake rates, especially for food items that contain high concentrations of fluoride (e.g., tea), are likely to be underestimated. For example, at an average fluoride concentration of 3.3 mg/L for brewed tea and 0.86 mg/L for iced tea (USDA 2004), the tea component in the background food presented in Table 2-9 represents an average daily consumption of one-half cup of brewed tea or 2 cups of iced tea. A habitual tea drinker, especially for brewed tea, can be expected to significantly exceed these con-

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FIGURE 2-2 Source contribution to total inorganic fluoride exposure, including fluoride at 2 mg/L fluoride in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures as presented in Table 2-11 for the population subgroups are: 0.046 mg/kg/day (nursing infants), 0.144 mg/kg/day (non-nursing infants), 0.090 mg/kg/day (1-2 years old), 0.082 mg/kg/day (3-5 years old), 0.055 mg/kg/day (6-12 years old), 0.039 mg/kg/day (13-19 years old), and 0.046-0.047 mg/kg/day for adults (20-50+ years old) and women of childbearing age (13-49 years old).

Other groups of people who are expected to have exposures higher than those calculated here include infants given fluoride toothpaste before age 1, anyone who uses toothpaste more than twice per day or who swallows excessive amounts of toothpaste, children inappropriately given fluoride supplements in a fluoridated area, children in an area with high fluoride concentrations in soil, and children with pica who consume large amounts of soil.

The exposure estimates presented in this chapter for non-drinking-water routes are based on the potential profile of fluoride residue concentrations...
FIGURE 2-3  Source contribution to total inorganic fluoride exposure, including fluoride at 4 mg/L in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures as presented in Table 2-11 for the population subgroups are: 0.079 mg/kg/day (nursing infants), 0.258 mg/kg/day (nonnursing infants), 0.137 mg/kg/day (1-2 years old), 0.126 mg/kg/day (3-5 years old), 0.086 mg/kg/day (6-12 years old), 0.063 mg/kg/day (13-19 years old), 0.075-0.079 mg/kg/day for adults (20-50+ years old) and women of childbearing age (13-49 years old).

in the current exposure media. They likely do not reflect the concentration of past exposure scenarios, particularly for routes that show changes in time (e.g., pesticide use practices). Any new and significant source of fluoride exposure, such as commodities approved for sulfuryl fluoride fumigation application beyond April 2005, is expected to alter the percentage of drinking water contribution as presented in this chapter.

Different assumptions for the drinking-water concentration alone also can result in slightly different estimates. For example, values in Table 2-11 are derived from assuming that the nontap water has a fixed fluoride concentration of 0.5 mg/L, while tap-water concentration varies up to 4 mg/L. Table 2-12 provides alternative calculations of total exposure by assuming
that all sources of drinking water (both tap and nontap water) contain the same specified fluoride concentration. Within this assumption, the drinking-water component can be estimated from either the DEEM-FCID model or the default drinking-water intake rate currently used by EPA for establishing the MCL (1 L/day for a 10-kg child and 2 L/day for a 70-kg adult). Some uncertainties exist regarding the extent the FCID database may include all processed waters (e.g., soft drinks and soups). Thus, the exposure using EPA's defaults as presented in Table 2-12 can serve as a bounding estimate from the water contribution. The difference in the total fluoride exposure calculated from the two water intake methods (i.e., EPA defaults versus FCID modeled) varies with different population subgroups shown in Table 2-12. In general, as the drinking-water contribution to the total exposure becomes more prominent at higher drinking-water concentration, the differences in total exposure approach the differences in drinking-water intake rates of the two methods. Using EPA's default adult water intake rate of 28.6 mL/kg/day (based on 2 L/day for a 70 kg adult) results in approximately 32-39% higher total exposure than the model estimates. This approximates the 38-45% lower model estimate of total water intake rate.

### TABLE 2-12  Total Estimated (Average) Chronic Inorganic Fluoride Exposure (mg/kg/day) from All Sources, Assuming the Same Specified Fluoride Concentration for Both Tap and Nontap Waters

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Concentration in All Water</th>
<th>Modeled water intake&lt;sup&gt;b&lt;/sup&gt;</th>
<th>EPA default water intake&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/L</td>
<td>2 mg/L</td>
<td>4 mg/L</td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.082</td>
<td>0.151</td>
<td>0.289</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.034</td>
<td>0.060</td>
<td>0.111</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.100</td>
<td>0.186</td>
<td>0.357</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.070</td>
<td>0.102</td>
<td>0.164</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>0.063</td>
<td>0.093</td>
<td>0.151</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>0.042</td>
<td>0.062</td>
<td>0.103</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
<td>0.030</td>
<td>0.045</td>
<td>0.075</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.034</td>
<td>0.053</td>
<td>0.093</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>0.034</td>
<td>0.054</td>
<td>0.096</td>
</tr>
<tr>
<td>Females 13-49 years&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.033</td>
<td>0.053</td>
<td>0.092</td>
</tr>
</tbody>
</table>

<sup>a</sup>The estimated exposures from nonwater sources (including pesticides, background food, air, and toothpaste) are from Table 2-9. No fluoride supplement is included in the total fluoride exposure estimates.

<sup>b</sup>The component of drinking-water exposure is estimated from DEEM-FCID.

<sup>c</sup>The EPA default daily water intake rate is 1 L for a 10-kg child and 2 L for a 70-kg adult. NA: not applicable based on EPA's default body weight.

<sup>d</sup>Women of childbearing age.
Using EPA’s default water intake rate for a child results in approximately 16% higher total exposure than the model estimates for nonnursing infants at 4 mg/L drinking water. This reflects closely the difference in the total water intake between the default 100 mL/kg/day (based on 1 L/day for a 10 kg child) and the DEEM-FCID estimate of 85.5 mL/kg/day for this population group. Similarly, for nursing infants, the 3.7-fold higher total exposure at 4 mg/L from using the EPA’s default of 100 mL/kg/day also reflects their significantly lower model estimate of total water intake (i.e., 25.6 mL/kg/day).

Two additional simple conceptual observations can be made to relate data presented in Table 2-12 to those in Tables 2-9 and 2-11. By using a fixed rate of water intake for infants and children 1-2 years old, the difference in their total exposure is due to the contribution from all nonwater sources as presented in Table 2-9. The difference between model estimates presented in Table 2-11 (last 3 columns) by varying concentrations for tap water alone (with fixed nontap water at 0.5 mg/L) and estimates using one fluoride concentration for both tap and nontap waters in Table 2-12 (first 3 columns) reflects the contribution from the nontap-water component.

The fluoride exposure estimates presented thus far, regardless of the various assumptions (e.g., the same versus different fluoride concentrations in tap and nontap water) and different water intake rates (e.g., EPA default versus estimates from FCID database of the CSFII surveys), do not include those who have sustained high water intake rates as noted previously (athletes, workers, and individuals with diabetes mellitus or nephrogenic diabetes insipidus (see Table 2-4). The high-end exposures for these high-water-consumption population subgroups are included in the summaries below.

**SUMMARY OF EXPOSURE ASSESSMENT**

The estimated aggregated total fluoride exposures from pesticides, background food, air, toothpaste, and drinking water are summarized for drinking water fluoride concentrations of 1 mg/L (Table 2-13), 2 mg/L (Table 2-14), and 4 mg/L (Table 2-15). Two sets of exposures are presented using different approaches to estimate the exposure from drinking water. One is estimated by modeling water intakes based on FCID data and assuming a fixed nontap water concentration of 0.5 mg/L. The other is estimated using EPA default drinking-water intake rates (i.e., 1 L/day for a 10 kg child, 2 L/day for a 70 kg adult) and assuming the same concentration for tap and nontap waters. Both sets of estimates include the same fluoride exposure from nonwater sources. The total exposure from the latter approach is higher than the model estimates due to the higher default drinking water intake rates and the assumption that nontap waters contain the same concentration of fluoride residue as the tap water.
### TABLE 2-13 Contributions to Total Fluoride Chronic Exposure at 1 mg/L in Drinking Water

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Total Exposure, mg/kg/day</th>
<th>% Contribution to Total Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pesticides and Air</td>
<td>Background Food</td>
</tr>
<tr>
<td>Modeled average water consumer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tap water at 1 mg/L, nontap water at 0.5 mg/L; Table 2-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.070</td>
<td>4.7</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.030</td>
<td>8.9</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.087</td>
<td>4.3</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.066</td>
<td>9.7</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>0.060</td>
<td>7.4</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>0.040</td>
<td>5.4</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
<td>0.028</td>
<td>4.9</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.031</td>
<td>4.0</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>0.031</td>
<td>4.4</td>
</tr>
<tr>
<td>Females 13-49 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.031</td>
<td>4.4</td>
</tr>
<tr>
<td>EPA default water intake, all water at 1 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 L/day for 10-kg child; 2 L/day for 70-kg adult; Table 2-12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.113</td>
<td>2.9</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.109</td>
<td>2.4</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.115</td>
<td>3.2</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.139</td>
<td>4.6</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.043</td>
<td>3.0</td>
</tr>
<tr>
<td>High end of high water intake individuals all water at 1 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(based on intake rates in Table 2-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Athletes and workers</td>
<td>0.084</td>
<td>1.5</td>
</tr>
<tr>
<td>DM patients (3-5 years)</td>
<td>0.134</td>
<td>3.3</td>
</tr>
<tr>
<td>DM patients (adults)</td>
<td>0.084</td>
<td>1.5</td>
</tr>
<tr>
<td>NDI patients (3-5 years)</td>
<td>0.184</td>
<td>2.4</td>
</tr>
<tr>
<td>NDI patients (adults)</td>
<td>0.164</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>Women of childbearing age.

**ABBREVIATIONS:** DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.

Although each of these exposure estimates have areas of uncertainty, the average total daily fluoride exposure is expected to fall between them. For the modeling estimates, there are inherent uncertainties in modeling long-term intake rates based on the cross-sectional CSFII dietary survey data. Thus, the exposure from any dietary component, water or other foods, could be underestimated for individuals who have habitually higher intake rates (e.g., water, tea). Specific to the water component, there are also uncertainties regarding the extent the FCID database may include all processed waters (e.g., soft drinks and soups). On the other hand, the EPA
TABLE 2-14 Contributions to Total Fluoride Chronic Exposure at 2 mg/L in Drinking Water

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Total Exposure, mg/kg/day</th>
<th>Pesticides and Air</th>
<th>Background Food</th>
<th>Toothpaste</th>
<th>Drinking Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modeled average water consumer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tap water at 2 mg/L, nontap water at 0.5 mg/L; Table 2-11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.117</td>
<td>2.8</td>
<td>8.2</td>
<td>0</td>
<td>89.0</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.046</td>
<td>5.8</td>
<td>10.1</td>
<td>0</td>
<td>81.0</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.144</td>
<td>2.6</td>
<td>7.9</td>
<td>0</td>
<td>89.5</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.090</td>
<td>7.1</td>
<td>23.3</td>
<td>12.8</td>
<td>56.7</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>0.082</td>
<td>5.4</td>
<td>22.1</td>
<td>13.9</td>
<td>58.6</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>0.055</td>
<td>3.9</td>
<td>22.4</td>
<td>13.7</td>
<td>60.1</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
<td>0.039</td>
<td>3.5</td>
<td>24.5</td>
<td>8.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.046</td>
<td>2.8</td>
<td>24.7</td>
<td>3.1</td>
<td>69.4</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>0.047</td>
<td>2.9</td>
<td>21.7</td>
<td>3.0</td>
<td>72.4</td>
</tr>
<tr>
<td>Females 13-49 years</td>
<td>0.046</td>
<td>3.0</td>
<td>23.4</td>
<td>3.6</td>
<td>70.1</td>
</tr>
</tbody>
</table>

EPA default water intake, all water at 1 mg/L
(2 L/day for 10-kg child; 2 L/day for 70-kg adult; Table 2-12)

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Total Exposure, mg/kg/day</th>
<th>Pesticides and Air</th>
<th>Background Food</th>
<th>Toothpaste</th>
<th>Drinking Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.213</td>
<td>1.6</td>
<td>4.5</td>
<td>0</td>
<td>93.9</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.209</td>
<td>1.3</td>
<td>2.2</td>
<td>0</td>
<td>95.8</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.215</td>
<td>1.7</td>
<td>5.3</td>
<td>0</td>
<td>93.0</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.239</td>
<td>2.7</td>
<td>8.8</td>
<td>4.8</td>
<td>83.7</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.071</td>
<td>1.8</td>
<td>16.0</td>
<td>2.0</td>
<td>80.2</td>
</tr>
</tbody>
</table>

High end of high water intake individuals all water at 2 mg/L
(based on intake rates in Table 2-4)

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Total Exposure, mg/kg/day</th>
<th>Pesticides and Air</th>
<th>Background Food</th>
<th>Toothpaste</th>
<th>Drinking Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athletes and workers</td>
<td>0.154</td>
<td>0.8</td>
<td>7.4</td>
<td>0.9</td>
<td>90.9</td>
</tr>
<tr>
<td>DM patients (3-5 years)</td>
<td>0.234</td>
<td>1.9</td>
<td>7.7</td>
<td>4.9</td>
<td>85.5</td>
</tr>
<tr>
<td>DM patients (adults)</td>
<td>0.154</td>
<td>0.8</td>
<td>7.4</td>
<td>0.9</td>
<td>90.9</td>
</tr>
<tr>
<td>NDI patients (3-5 years)</td>
<td>0.334</td>
<td>1.3</td>
<td>5.4</td>
<td>3.4</td>
<td>89.9</td>
</tr>
<tr>
<td>NDI patients (adults)</td>
<td>0.314</td>
<td>0.4</td>
<td>3.6</td>
<td>0.5</td>
<td>95.5</td>
</tr>
</tbody>
</table>

Women of childbearing age.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.

default water intake rate is likely higher than the average rate for certain population subgroups (e.g., nursing infants).

The estimates presented in Tables 2-13, 2-14, and 2-15 show that on a per body weight basis, the exposures are generally higher for young children than for the adults. By assuming that the nontap water concentration is fixed at 0.5 mg/L, nonnursing infants have the highest model-estimated average total daily fluoride exposure: 0.087, 0.144, and 0.258 mg/kg/day when tap-water concentrations of fluoride are 1, 2, and 4 mg/L, respectively (Table
### TABLE 2-15 Contributions to Total Fluoride Chronic Exposure at 4 mg/L in Drinking Water

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Total Exposure, mg/kg/day</th>
<th>% Contribution to Total Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pesticides and Air</td>
<td>Background Food</td>
</tr>
<tr>
<td>Modeled average water consumer (Tap water at 4 mg/L, nontap water at 0.5 mg/L; Table 2-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infants (&lt;1 year)</td>
<td>0.209</td>
<td>1.6</td>
</tr>
<tr>
<td>Nursing</td>
<td>0.079</td>
<td>3.3</td>
</tr>
<tr>
<td>Nonnursing</td>
<td>0.258</td>
<td>1.4</td>
</tr>
<tr>
<td>Children 1-2 years</td>
<td>0.137</td>
<td>4.7</td>
</tr>
<tr>
<td>Children 3-5 years</td>
<td>0.126</td>
<td>3.5</td>
</tr>
<tr>
<td>Children 6-12 years</td>
<td>0.086</td>
<td>2.5</td>
</tr>
<tr>
<td>Youth 13-19 years</td>
<td>0.063</td>
<td>2.2</td>
</tr>
<tr>
<td>Adults 20-49 years</td>
<td>0.076</td>
<td>1.7</td>
</tr>
<tr>
<td>Adults 50+ years</td>
<td>0.079</td>
<td>1.7</td>
</tr>
<tr>
<td>Females 13-49 years(a)</td>
<td>0.075</td>
<td>1.8</td>
</tr>
</tbody>
</table>

EPA default water intake all water at 4 mg/L (1 L/day for 10-kg child; 2 L/day for 70-kg adult; Table 2-12)

| All infants (<1 year)         | 0.413                     | 0.8                               | 2.3        | 0              | 96.9          |
| Nursing                       | 0.409                     | 0.6                               | 1.1        | 0              | 97.9          |
| Nonnursing                    | 0.415                     | 0.9                               | 2.8        | 0              | 96.4          |
| Children 1-2 years            | 0.439                     | 1.5                               | 4.8        | 2.6            | 91.1          |
| Adults 20-49 years            | 0.128                     | 1.0                               | 8.9        | 1.1            | 89.0          |

High end of high water intake individuals, all water at 4 mg/L (based on intake rates in Table 2-4)

| Athletes and workers          | 0.294                     | 0.4                               | 3.9        | 0.5            | 95.2          |
| DM patients (3-5 years)       | 0.434                     | 1.0                               | 4.2        | 2.6            | 92.2          |
| DM patients (adults)          | 0.294                     | 0.4                               | 3.9        | 0.5            | 95.2          |
| NDI patients (3-5 years)      | 0.634                     | 0.7                               | 2.9        | 1.8            | 94.7          |
| NDI patients (adults)         | 0.614                     | 0.2                               | 1.9        | 0.2            | 97.7          |

\(a\)Women of childbearing age.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus

The major contributing factor is their much higher model-estimated drinking-water exposure than other age groups (Table 2-10). The total exposures of nonnursing infants are approximately 2.8-3.4 times that of adults. By holding the exposure from drinking water at a constant with the EPA default water intake rates, children 1-2 years old have slightly higher total exposure than the nonnursing infants, reflecting the higher exposure from nonwater sources (Table 2-9). The estimated total fluoride exposures for children 1-2 years old are 0.139, 0.239,
and 0.439 mg/kg/day for 1, 2, and 4 mg/L of fluoride in drinking water, respectively (Tables 2-13, 2-14, 2-15). These exposures are approximately 3.4 times that of adults. The estimated total exposure for children 1-2 years old and adults at 4 mg/L fluoride in drinking water is approximately two times the exposure at 2 mg/L and three times the exposure at 1 mg/L.

The estimated total daily fluoride exposures for three population subgroups with significantly high water intake rates are included in Tables 2-13, 2-14, and 2-15. The matching age groups for data presented in Table 2-4 are: adults ≥ 20 years old for the athletes and workers, and both children 3-5 years old (default body weight of 22 kg) and adults for individuals with diabetes mellitus and nephrogenic diabetes insipidus. In estimating the total exposure, the high-end water intake rates from Table 2-4 are used to calculate the exposure from drinking water. The total exposures for adult athletes and workers are 0.084, 0.154, and 0.294 mg/kg/day at 1, 2, and 4 mg/L of fluoride in water, respectively. These doses are approximately two times those of the adults with a default water intake rate of 2 L/day. For individuals with nephrogenic diabetes insipidus, the respective total fluoride exposures for children (3-5 years old) and adults are 0.184 and 0.164 mg/kg/day at 1 mg/L, 0.334 and 0.314 mg/kg/day at 2 mg/L, and 0.634 and 0.614 mg/kg/day at 4 mg/L. Compared to the exposure of children 1-2 years old, who have the highest total exposure among all age groups of the general population (i.e., 0.139-0.439 mg/kg/day at 1-4 mg/L, assuming EPA’s 100 mL/kg/day default water intake rate for children), the highest estimated total exposure among these high water intake individuals (i.e., 0.184-0.634 mg/kg/day for children 3-5 years old with nephrogenic diabetes insipidus, assuming 150 mL/kg/day high-end water intake rate) are 32-44% higher.

The relative contributions from each source of exposure are also presented in Tables 2-13, 2-14, and 2-15. For an average individual, the model-estimated drinking-water contribution to the total fluoride exposure is 41-83% at 1 mg/L in tap water, 57-90% at 2 mg/L, and 72-94% at 4 mg/L in tap water (see also Figures 2-1, 2-2, and 2-3). Assuming that all drinking-water sources (tap and nontap) contain the same fluoride concentration and using the EPA default drinking-water intake rates, the drinking-water contribution is 67-92% at 1 mg/L, 80-96% at 2 mg/L, and 89-98% at 4 mg/L. The drinking-water contributions for the high water intake individuals among adult athletes and workers, and individuals with diabetes mellitus and nephrogenic diabetes insipidus, are 75-91% at 1 mg/L, 86-96% at 2 mg/L, and 92-98% at 4 mg/L.

As noted earlier, these estimates were based on the information that was available to the committee as of April 2005. Any new and significant sources of fluoride exposure are expected to alter the percentage of drinking-water contribution as presented in this chapter. However, water will still be the most significant source of exposure.
BIOMARKERS OF EXPOSURE, EFFECT, AND SUSCEPTIBILITY

Biological markers, or biomarkers, are broadly defined as indicators of variation in cellular or biochemical components or processes, structure, or function that are measurable in biological systems or samples (NRC 1989a). Biomarkers often are categorized by whether they indicate exposure to an agent, an effect of exposure, or susceptibility to the effects of exposure (NRC 1989a). Vine (1994) described categories of biological markers in terms of internal dose, biologically effective dose, early response, and disease, plus susceptibility factors that modify the effects of the exposure. Factors that must be considered in selecting a biomarker for a given study include the objectives of the study, the availability and specificity of potential markers, the feasibility of measuring the markers (including the invasiveness of the necessary techniques and the amount of biological specimen needed), the time to appearance and the persistence of the markers in biological media, the variability of marker concentrations within and between individuals, and aspects (e.g., cost, sensitivity, reliability) related to storage and analysis of the samples (Vine 1994). ATSDR (2003) recently reviewed biomarkers of exposure and effect for fluoride.

Biomarkers of exposure to fluoride consist of measured fluoride concentrations in biological tissues or fluids that can be used as indices of an individual’s exposure to fluoride. For fluoride, concentrations in a number of tissues and fluids, including teeth, bones, nails, hair, urine, blood or plasma, saliva, and breast milk, have been used to estimate exposures (Vine 1994; Whitford et al. 1994; ATSDR 2003). Table 2-16 gives examples of measurements in humans together with the associated estimates of exposure. The Centers for Disease Control and Prevention (CDC 2003, 2005) has measured a number of chemicals in blood or urine of members of the U.S. population, but thus far fluoride has not been included in their survey.

Fluoride concentrations in bodily fluids (e.g., urine, plasma, serum, saliva) are probably most suitable for evaluating recent or current fluoride exposures or fluoride balance (intake minus excretion), although some sources indicate that samples obtained from fasting persons may be useful for estimating chronic fluoride intake or bone fluoride concentrations (e.g., Ericsson et al. 1973; Waterhouse et al. 1980). Examples of the association between estimated fluoride intakes (or mass-normalized intakes) and measured fluoride concentrations in urine, plasma, and serum for individuals and groups are shown in Figures 2-4, 2-5, 2-6, and 2-7. Note that in most cases, the variation in fluoride intake is not sufficient to explain the variation in the measured fluoride concentrations. A number of parameters affect individual fluoride uptake, retention, and excretion (Chapter 3) (Whitford 1996). In addition, a significant decrease in fluoride exposure might not be
TABLE 2-16 Summary of Selected Biomarkers for Fluoride Exposure in Humans

<table>
<thead>
<tr>
<th>Fluoride Exposure</th>
<th>Number of Persons</th>
<th>Fluoride Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2-2.2 mg/day</td>
<td>5</td>
<td>0.8-1.2 mg/day</td>
<td>Teotia et al. 1978</td>
</tr>
<tr>
<td>2.5-3.8 mg/day</td>
<td>2</td>
<td>1.2-2.2 mg/day</td>
<td>(Figure 2-4)</td>
</tr>
<tr>
<td>8.7-9.2 mg/day</td>
<td>3</td>
<td>3.2-5.8 mg/day</td>
<td></td>
</tr>
<tr>
<td>21.0-28.0 mg/day</td>
<td>2</td>
<td>10.0-11.0 mg/day</td>
<td></td>
</tr>
<tr>
<td>48.0-52.0 mg/day</td>
<td>2</td>
<td>15.0-18.5 mg/day</td>
<td></td>
</tr>
<tr>
<td>1.0 mg/L in drinking water</td>
<td>17</td>
<td>1.5 (0.2) mg/L</td>
<td>Bachinskii et al. 1985</td>
</tr>
<tr>
<td>2.3 mg/L in drinking water</td>
<td>30</td>
<td>2.4 (0.2) mg/L</td>
<td>(Figure 2-6)</td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>0.15 (0.07) mg/L</td>
<td>Schamschula et al. 1985 (Figure 2-6)</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>0.62 (0.26) mg/L</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>1.24 (0.52) mg/L</td>
<td></td>
</tr>
<tr>
<td>0.32 mg/L in drinking water</td>
<td>100</td>
<td>0.77 (0.49) mg/L</td>
<td>Czarnowski et al. 1999</td>
</tr>
<tr>
<td>1.69 mg/L in drinking water</td>
<td>111</td>
<td>1.93 (0.82) mg/L</td>
<td>(Figure 2-6)</td>
</tr>
<tr>
<td>2.74 mg/L in drinking water</td>
<td>89</td>
<td>2.89 (1.39) mg/L</td>
<td></td>
</tr>
<tr>
<td>About 3 mg/day</td>
<td>1</td>
<td>2.30-2.87 mg/day</td>
<td>Whitford et al. 1999a</td>
</tr>
<tr>
<td>About 6 mg/day</td>
<td>1</td>
<td>4.40-5.13 mg/day</td>
<td></td>
</tr>
<tr>
<td>7.35 (1.72) mg/day</td>
<td>50</td>
<td>9.45 (4.11) mg/L</td>
<td>Gupta et al. 2001</td>
</tr>
<tr>
<td>11.97 (1.8) mg/day</td>
<td>50</td>
<td>15.9 (9.98) mg/L</td>
<td>(Figure 2-7)</td>
</tr>
<tr>
<td>14.45 (3.19) mg/day</td>
<td>50</td>
<td>17.78 (7.77) mg/L</td>
<td></td>
</tr>
<tr>
<td>32.56 (9.33) mg/day</td>
<td>50</td>
<td>14.56 (7.88) mg/L</td>
<td></td>
</tr>
<tr>
<td>0.93 (0.39) mg/day [0.053 (0.021) mg/kg/day]</td>
<td>11</td>
<td>0.91 (0.45) mg/L</td>
<td>Haftenberger et al. 2001 (Figure 2-5)</td>
</tr>
<tr>
<td>1.190 (0.772) mg/day from all sources</td>
<td>20</td>
<td>0.481 (0.241) mg/day</td>
<td>Pesson et al. 2005</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2-2.2 mg/day</td>
<td>5</td>
<td>0.020-0.038 mg/L</td>
<td>Teotia et al. 1978</td>
</tr>
<tr>
<td>2.5-3.8 mg/day</td>
<td>2</td>
<td>0.036-0.12 mg/L</td>
<td>(Figure 2-4)</td>
</tr>
<tr>
<td>8.7-9.2 mg/day</td>
<td>3</td>
<td>0.15-0.18 mg/L</td>
<td></td>
</tr>
<tr>
<td>21.0-28.0 mg/day</td>
<td>2</td>
<td>0.11-0.17 mg/L</td>
<td></td>
</tr>
<tr>
<td>48.0-52.0 mg/day</td>
<td>2</td>
<td>0.14-0.26 mg/L</td>
<td></td>
</tr>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg/L in drinking water</td>
<td>17</td>
<td>0.21 (0.01) mg/L</td>
<td>Bachinskii et al. 1985</td>
</tr>
<tr>
<td>2.3 mg/L in drinking water</td>
<td>30</td>
<td>0.25 (0.01) mg/L</td>
<td>(Figure 2-6)</td>
</tr>
<tr>
<td>7.35 (1.72) mg/day</td>
<td>50</td>
<td>0.79 (0.21) mg/L</td>
<td>Gupta et al. 2001</td>
</tr>
<tr>
<td>11.97 (1.8) mg/day</td>
<td>50</td>
<td>1.10 (0.58) mg/L</td>
<td>(Figure 2-7)</td>
</tr>
<tr>
<td>14.45 (3.19) mg/day</td>
<td>50</td>
<td>1.10 (0.17) mg/L</td>
<td></td>
</tr>
<tr>
<td>32.56 (9.33) mg/day</td>
<td>50</td>
<td>1.07 (0.17) mg/L</td>
<td></td>
</tr>
<tr>
<td>Fluoride Exposure</td>
<td>Number of Persons</td>
<td>Fluoride Concentration</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Breastfed infants</td>
<td>48</td>
<td>0.0042 (0.0027) mg/L</td>
<td>Hossny et al. 2003</td>
</tr>
<tr>
<td>All infants (4 weeks-2 years)</td>
<td>97</td>
<td>0.0051 (0.0030) mg/L</td>
<td></td>
</tr>
<tr>
<td>Preschoolers (2-6 years)</td>
<td>100</td>
<td>0.011 (0.0049) mg/L</td>
<td></td>
</tr>
<tr>
<td>Primary schoolers (6-12 years)</td>
<td>99</td>
<td>0.010 (0.0042) mg/L</td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>6.25 (2.44) µg/L</td>
<td>Schamschula et al. 1985</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>11.23 (4.29) µg/L</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>15.87 (6.01) µg/L</td>
<td></td>
</tr>
<tr>
<td>0.1 mg/L in drinking water</td>
<td>27</td>
<td>1.9-55.1 µg/L</td>
<td>Oliveby et al. 1990</td>
</tr>
<tr>
<td>1.2 mg/L in drinking water</td>
<td>27</td>
<td>1.9-144 µg/L</td>
<td>Oliveby et al. 1990</td>
</tr>
<tr>
<td>Plaque</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>5.04 (4.60) ppm</td>
<td>Schamschula et al. 1985</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>8.47 (9.69) ppm</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>19.6 (19.3) ppm</td>
<td></td>
</tr>
<tr>
<td>Hair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>0.18 (0.07) µg/g</td>
<td>Schamschula et al. 1985</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>0.23 (0.11) µg/g</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>0.40 (0.25) µg/g</td>
<td></td>
</tr>
<tr>
<td>0.27 mg/L in drinking water and 2.8 µg/m³ in air</td>
<td>59</td>
<td>1.35 (0.95) µg/g</td>
<td>Hac et al. 1997</td>
</tr>
<tr>
<td>0.32 mg/L in drinking water</td>
<td>53</td>
<td>4.13 (2.24) µg/g</td>
<td>Czarnowski et al. 1999</td>
</tr>
<tr>
<td>1.69 mg/L in drinking water</td>
<td>111</td>
<td>10.25 (6.63) µg/g</td>
<td></td>
</tr>
<tr>
<td>2.74 mg/L in drinking water</td>
<td>84</td>
<td>14.51 (6.29) µg/g</td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>47</td>
<td>0.0053 mg/L (colostrum)</td>
<td>Spak et al. 1983</td>
</tr>
</tbody>
</table>

continued
<table>
<thead>
<tr>
<th>Fluoride Exposure</th>
<th>Number of Persons</th>
<th>Fluoride Concentration Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg/L in drinking water</td>
<td>79</td>
<td>0.0068 mg/L (colostrum)</td>
</tr>
<tr>
<td>1.0 mg/L in drinking water</td>
<td>17</td>
<td>0.007 mg/L (mature milk)</td>
</tr>
<tr>
<td>Nonfluoridated community</td>
<td>32</td>
<td>0.0044 mg/L</td>
</tr>
<tr>
<td>1 mg/L in drinking water</td>
<td>112</td>
<td>0.0098 mg/L</td>
</tr>
<tr>
<td>22.1 mg/day (mean)</td>
<td>27</td>
<td>0.011-0.073 mg/L</td>
</tr>
<tr>
<td>0.3 mg/L in drinking water</td>
<td>60</td>
<td>0.0046 (0.0025) mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingernails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>0.79 (0.26) ppm&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>1.31 (0.49) ppm&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>2.31 (1.14) ppm&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>About 3 mg/day</td>
<td>1</td>
<td>1.94-3.05 mg/kg</td>
</tr>
<tr>
<td>About 6 mg/day (after 3.5 months)</td>
<td>1</td>
<td>4.52-5.38 mg/kg</td>
</tr>
<tr>
<td>0.1 mg/L in drinking water</td>
<td>10</td>
<td>0.75-3.53 mg/kg</td>
</tr>
<tr>
<td>1.6 mg/L in drinking water</td>
<td>6</td>
<td>2.28-7.53 mg/kg</td>
</tr>
<tr>
<td>2.3 mg/L in drinking water</td>
<td>9</td>
<td>4.00-13.18 mg/kg</td>
</tr>
<tr>
<td>0.7-1.0 mg/L in drinking water, without fluoride dentifrice</td>
<td>10</td>
<td>2.3-7.3 mg/kg</td>
</tr>
<tr>
<td>0.7-1.0 mg/L in drinking water, with fluoride dentifrice (after 4 months)</td>
<td>10</td>
<td>10.1 mg/kg (peak)</td>
</tr>
<tr>
<td>0.004 ± 0.003 mg/kg/day</td>
<td>15</td>
<td>0.42-6.11 µg/g</td>
</tr>
<tr>
<td>0.029 ± 0.029 mg/kg/day</td>
<td>15</td>
<td>0.87-7.06 µg/g</td>
</tr>
<tr>
<td>Toenails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 mg/L in drinking water</td>
<td></td>
<td>4.2 ppm</td>
</tr>
<tr>
<td>1.0 mg/L in drinking water</td>
<td></td>
<td>6.4 ppm</td>
</tr>
<tr>
<td>3 mg/day</td>
<td>1</td>
<td>1.41-1.60 mg/kg</td>
</tr>
<tr>
<td>0.7-1.0 mg/L in drinking water, without fluoride dentifrice</td>
<td>10</td>
<td>2.5-5.6 mg/kg</td>
</tr>
<tr>
<td>0.7-1.0 mg/L in drinking water, with fluoride dentifrice (after 4 months)</td>
<td>10</td>
<td>9.2 mg/kg (peak)</td>
</tr>
<tr>
<td>0.004 ± 0.003 mg/kg/day</td>
<td>15</td>
<td>0.08-3.89 µg/g</td>
</tr>
<tr>
<td>0.029 ± 0.029 mg/kg/day</td>
<td>15</td>
<td>0.81-6.38 µg/g</td>
</tr>
<tr>
<td>Teeth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>NA</td>
<td>190-300 ppm (total ash)</td>
</tr>
</tbody>
</table>

<sup>b</sup>Whitford et al. 1999a
<sup>b</sup>Corrêa Rodrigues et al. 2004
<sup>b</sup>Levy et al. 2004
<sup>b</sup>Feskanich et al. 1998
<sup>b</sup>Whitford et al. 1999a
<sup>b</sup>Corrêa Rodrigues et al. 2004
<sup>b</sup>Levy et al. 2004

Roholm 1937
### TABLE 2-16 Continued

<table>
<thead>
<tr>
<th>Fluoride Exposure</th>
<th>Number of Persons</th>
<th>Fluoride Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryolite workers</td>
<td>5</td>
<td>1,100-5,300 ppm (total ash)</td>
<td></td>
</tr>
<tr>
<td>Enamel (0.44-0.48 μm depth)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>1,549 (728) ppm\textsuperscript{b}</td>
<td>Schamschula et al. 1985</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>2,511 (1,044) ppm\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>3,792 (1,362) ppm\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>Enamel (2.44-2.55 μm depth)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.09 (range, 0.06-0.11) mg/L in drinking water</td>
<td>45</td>
<td>641 (336) ppm\textsuperscript{b}</td>
<td>Schamschula et al. 1985</td>
</tr>
<tr>
<td>0.82 (range, 0.5-1.1) mg/L in drinking water</td>
<td>53</td>
<td>1,435 (502) ppm\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>1.91 (range, 1.6-3.1) mg/L in drinking water</td>
<td>41</td>
<td>2,107 (741) ppm\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>Enamel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7 or 1.0 mg/L in drinking water</td>
<td>30</td>
<td>0-192 µg/g</td>
<td>Vieira et al. 2005</td>
</tr>
<tr>
<td>Dentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7 or 1.0 mg/L in drinking water</td>
<td>30</td>
<td>59-374 µg/g</td>
<td>Vieira et al. 2005</td>
</tr>
<tr>
<td>Bones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>NA</td>
<td>480-2,100 ppm in bone ash (ribs)</td>
<td>Roholm 1937</td>
</tr>
<tr>
<td>Cryolite workers</td>
<td>2</td>
<td>9,900 and 11,200 ppm in bone ash (ribs) ranges (ppm in bone ash, various bone types, 3,100-9,900 and 8,100-13,100 in the 2 individuals</td>
<td></td>
</tr>
<tr>
<td>0.1-0.4 mg/L in drinking water</td>
<td>33</td>
<td>326-2,390 ppm in bone ash\textsuperscript{a}</td>
<td>Zipkin et al. 1958</td>
</tr>
<tr>
<td>1.0 mg/L in drinking water</td>
<td>5</td>
<td>1,610-4,920 ppm in bone ash\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>2.6 mg/L in drinking water</td>
<td>27</td>
<td>1,560-10,800 ppm in bone ash\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>4.0 mg/L in drinking water</td>
<td>4</td>
<td>4,780-11,000 ppm in bone ash\textsuperscript{a}</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Includes bone minerals and bone ash.

\textsuperscript{b} Includes enamel.

\textsuperscript{c} Includes bone ash.

\textsuperscript{d} Includes ash.

\textsuperscript{e} Includes bone and ash.

\textsuperscript{f} Includes bone ash.

\textsuperscript{g} Includes ash.

\textsuperscript{h} Includes bone and ash.

\textsuperscript{i} Includes bone.

\textsuperscript{j} Includes ash.

\textsuperscript{k} Includes bone and ash.

\textsuperscript{l} Includes bone.

\textsuperscript{m} Includes ash.

\textsuperscript{n} Includes bone and ash.

\textsuperscript{o} Includes bone.

\textsuperscript{p} Includes ash.

\textsuperscript{q} Includes bone and ash.

\textsuperscript{r} Includes bone.

\textsuperscript{s} Includes ash.

\textsuperscript{t} Includes bone and ash.

\textsuperscript{u} Includes bone.

\textsuperscript{v} Includes ash.

\textsuperscript{w} Includes bone and ash.

\textsuperscript{x} Includes bone.

\textsuperscript{y} Includes ash.

\textsuperscript{z} Includes bone and ash.
### TABLE 2-16 Continued

<table>
<thead>
<tr>
<th>Fluoride Exposure</th>
<th>Number of Persons</th>
<th>Fluoride Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2 mg/L in drinking water since infancy</td>
<td>8</td>
<td>1,379 (179) ppm in bone ash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Eble et al. 1992</td>
</tr>
<tr>
<td>1 mg/L in drinking water at least 23 years or since infancy</td>
<td>9</td>
<td>1,775 (313) ppm in bone ash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Eble et al. 1992</td>
</tr>
<tr>
<td>0.27 mg/L in drinking water and 2.8 µg/m&lt;sup&gt;3&lt;/sup&gt; in air</td>
<td>59</td>
<td>625.7 (346.5) ppm&lt;sup&gt;b,h&lt;/sup&gt;</td>
<td>Hac et al. 1997</td>
</tr>
<tr>
<td>0.7 or 1.0 mg/L in drinking water</td>
<td>30</td>
<td>0.396 ppm&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Vieira et al. 2005</td>
</tr>
</tbody>
</table>

<sup>a</sup>Previous exposure of 30-38 mg/day, 2-5 years before study.  
<sup>b</sup>Mean and standard deviation.  
<sup>c</sup>Reported as 0.019-0.119% in bone, with ash content of 43.2-68.4%.  
<sup>d</sup>Reported as 0.100-0.238% in bone, with ash content of 45.9-62.2%.  
<sup>e</sup>Reported as 0.092-0.548% in bone, with ash content of 32.7-66.7%.  
<sup>f</sup>Reported as 0.261-0.548% in bone, with ash content of 32.7-66.7%.  
<sup>g</sup>Mean and standard error of the mean.  
<sup>h</sup>Reported as µg fluoride per gram bone; appears to be dry weight of bone, not bone ash.  
<sup>i</sup>Measured by Instrumental Neutron Activation Analysis; appears to be wet weight of bone.

ABBREVIATION: NA, not available.

Reflected immediately in urine or plasma, presumably because of remobilization of fluoride from resorbed bone.<sup>14</sup>

Concentrations of salivary fluoride (as excreted by the glands) are typically about two-thirds of the plasma fluoride concentration and independent of the salivary flow rate (Rölla and Ekstrand 1996); fluoride in the mouth from dietary intake or dentifrices also affects the concentrations measured in whole saliva. Significantly higher concentrations of fluoride were found in whole saliva and plaque following use of a fluoridated dentifrice versus a nonfluoridated dentifrice by children residing in an area with low fluoride (<0.1 mg/L) in drinking water. Concentrations were 15 times higher in whole saliva and 3 times higher in plaque, on average, 1 hour after use of the dentifrice (Whitford et al. 2005). Whitford et al. (1999b) found that whole-saliva fluoride concentrations in 5- to 10-year-old children were not signifi-

<sup>14</sup>For example, following defluoridation of a town’s water supply from 8 mg/L to around 1.3 mg/L (mean daily fluoride content over 113 weeks), urinary fluoride concentrations in males fell from means of 6.5 (children) and 7.7 (adults) mg/L before defluoridation to 4.9 and 5.1 mg/L, respectively, after 1 week, 3.5 and 3.4 mg/L, respectively, after 39 weeks, and 2.2 and 2.5 mg/L, respectively, after 113 weeks (Likins et al. 1956). An estimate of current fluoride intake (as opposed to fluoride balance) from a urine sample during this period would probably have been an overestimate.
FIGURE 2-4 Urinary fluoride excretion (left) and fasting plasma fluoride concentration (right) as functions of current daily fluoride intake for individual adults (nine males, five females) aged 18-58 years. Data from Teotia et al. 1978.

Significantly related to those in either plasma or parotid ductal saliva. However, fluoride concentrations in parotid ductal saliva were strongly correlated to the plasma fluoride concentrations ($r = 0.916$), with a saliva-to-plasma fluoride concentration ratio of 0.80 ($SE = 0.03$, range from 0.61 to 1.07). For three-quarters of the study population (13 of 17), the fluoride concentration in parotid ductal saliva could be used to estimate plasma fluoride concentrations within 20% or less, and the largest difference was 32%.

Measured fluoride concentrations in human breast milk have been correlated with the mother’s fluoride intake in some studies (Dabeka et al. 1986) and not well correlated in other studies (Spak et al. 1983; Opinya et al. 1991). In general, measurements of fluoride in breast milk would be of limited use in exposure estimation because of the very low concentrations even in cases of high fluoride intake, lack of a consistent correlation with the mother’s fluoride intake, and limitation of use to those members of a population who are lactating at the time of sampling.

Schamschula et al. (1985) found increasing concentrations of fluoride in urine, nails, hair, and saliva with increasing water fluoride concentration in a sample of Hungarian children, but fluoride contents were not directly proportional to the water fluoride content. Although means were significantly different between groups, there was sufficient variability among individuals within groups that individual values between groups overlapped. Feskanich et al. (1998) used toenail fluoride as an indicator of long-term...
Fluoride intake and considered it to be a better long-term marker than plasma concentrations. Whitford et al. (1999a) found a direct relationship between fluoride concentrations in drinking water and fluoride concentrations in fingernail clippings from 6- to 7-year-old children with no known fluoride exposure other than from drinking water. In nail samples from one adult, Whitford et al. (1999a) also found that an increase in fluoride intake was reflected in fingernail fluoride concentrations approximately 3.5 months later and that toenails had significantly lower fluoride concentrations than fingernails. Levy et al. (2004) also found higher fluoride concentrations in fingernails.
FIGURE 2-6 Urinary (left) and serum (right) fluoride concentrations as functions of fluoride concentration in drinking water. Dark symbols indicate means of groups; vertical lines indicate 1 standard deviation from the mean. Data from Bachinskii et al. (1985; circles), Schamschula et al. (1985; diamonds), and Czarnowski et al. (1999; triangles). Data from Bachinskii et al. represent 47 adults (ages 19-59); data from Schamschula et al. represent children aged 14 years; and data from Czarnowski et al. represent adults (ages 24-77, mean age 50).

FIGURE 2-7 Urinary (left) and serum (right) fluoride concentrations as functions of estimated daily fluoride intake (data from Gupta et al. 2001). Dark circles indicate means of groups of 50 children (ages 6-12); vertical lines indicate 1 standard deviation from the mean.
than in toenails in 2- to 6-year old children and showed a correlation between nail concentrations and dietary fluoride intake (exclusive of fluoride in toothpaste). Plasma fluoride in these children was not correlated with fluoride in fingernails, toenails, diet, or drinking water.

In contrast, Corrêa Rodrigues et al. (2004), in samples from 2- to 3-year-old children, found no significant differences in fluoride concentrations between fingernails and toenails collected at the same time. An increase in fluoride intake in these children was reflected in nail samples approximately 4 months later (Corrêa Rodrigues et al. 2004). Most likely, differences in “lag times” and differences between fingernails and toenails in the same individual reflect differences in growth rates of the nails due to factors such as age or differences in blood flow. McDonnell et al. (2004) found a wide variation in growth rates of thumbnails of 2- and 3-year-old children; age, gender, and fluoride exposure had no effect on the growth rates. However, it was emphasized that, for any study in which it is of interest to estimate the timing of a fluoride exposure based on measurements of fluoride in nails, the growth rate of the nails should be measured for each individual.

Czarnowski et al. (1999) found correlations between water fluoride concentrations and urinary fluoride, fluoride in hair, and bone mineral density measured in 300 people in the Gdánsk region of Poland. For workers with occupational exposure to airborne fluoride (largely HF), Czarnowski and Krechniak (1990) found good correlation among groups of workers between fluoride concentrations in urine and nails (r = 0.99); correlation between concentrations in urine and hair or hair and nails was also positive but not as good (r = 0.77 and 0.70, respectively). For individual values, positive correlation was found only between concentrations in urine and nails (r = 0.73). It was not possible to establish correlations between fluoride concentrations in biological media and air (Czarnowski and Krechniak 1990).

Measuring the fluoride content of teeth and bones can give an indication of chronic or cumulative fluoride exposure, although after cessation of fluoride exposure, bone fluoride concentrations slowly decrease because of resorption of bone. In addition, bone turnover results in the accumulation of various concentrations of fluoride in different bone types and sites (Selwitz 1994). Dentin has also been suggested as a reasonably accurate marker for long-term exposure (Selwitz 1994), although Vieira et al. (2005) found no correlation between bone fluoride and either enamel or dentin fluoride in persons with exposure to 0.07 or 1.0 mg/L fluoride in drinking water.

Roholm (1937) reported that the fluoride content in normal teeth varied from 190 to 300 ppm (0.19 to 0.30 mg/g) in the total ash, with 5-7 times as much fluoride in the dentin as in the enamel. Fluoride content in the total ash of teeth from five cryolite workers (employed 8-10 years; three with osteosclerosis) contained 1,100-5,300 ppm (1.1-5.3 mg/g), with the most carious teeth containing the most fluoride. Roholm (1937) also reported
normal bone fluoride concentrations of 480-2,100 ppm in bone ash (0.48-
2.1 mg/g bone ash in ribs), with concentrations between 3,100 and 13,100
ppm in bone ash (3.1 and 13.1 mg/g bone ash; varying with type of bone)
in two cryolite workers. Hodge and Smith (1965), summarizing several
reports, listed mean concentrations of bone fluoride in normal individuals
between 450 and 1,200 ppm in bone ash and in people “suffering excessive
exposure” to fluorides between 7,500 and 20,830 ppm in bone ash. More
recently, Eble et al. (1992) have reported fluoride concentrations in bone
ash ranging from 378 ppm (16-year old with <0.2 mg/L fluoride in drinking
water since infancy) to 3,708 ppm (79-year old with fluoridated water). A
46-year old female with chronic renal failure had a fluoride concentration

The data of Zipkin et al. (1958) shows a good relationship between
drinking-water fluoride and the mean percentage of fluoride in bone (iliac
crest, rib, and vertebra) for adults in areas of various fluoride concentra-
tions in drinking water. However, the ranges (Table 2-16; see also Chapter
3, Figure 3-1) suggest that variability among individuals within groups
could be large, probably reflecting variability in individual fluoride intakes,
duration of exposure, and age. A major disadvantage of measuring bone
fluoride is the invasiveness of bone sampling in live individuals. Although
easier to do, x-ray screening for increased bone density should be done only
when the need for information justifies the radiation dose involved; in ad-
dition, bone density might not be related solely to fluoride exposure or to
bone fluoride content.

The two most important biomarkers of effect for fluoride are consid-
ered to be enamel fluorosis and skeletal fluorosis (ATSDR 2003); these are
discussed more fully in Chapters 4 and 5. Enamel fluorosis is characterized
by mottling and erosion of the enamel of the teeth and is associated with
elevated fluoride intakes during the childhood years when the teeth are
developing. According to the U.S. Public Health Service (PHS 1991), both
the percent prevalence and the increasing severity of enamel fluorosis are
associated with increasing fluoride concentration in drinking water (and
presumably actual fluoride intake). For “optimally” fluoridated water (0.7-
1.2 mg/L), 22% of children examined in the 1980s showed some fluorosis
(mostly very mild or mild); at water fluoride concentrations above 2.3 mg/L,
more than 70% of children showed fluorosis (PHS 1991; NRC 1993). Some
children developed fluorosis even at the lowest fluoride concentrations (<0.4
mg/L), suggesting that either fluoride intakes are variable within a popula-
tion with the same water supply or there is variability in the susceptibility
to fluorosis within populations (or both). Baelum et al. (1987) indicated
that 0.03 mg/kg/day might not be protective against enamel fluorosis, and
Fejerskov et al. (1987) stated that the borderline dose above which enamel
fluorosis might develop could be as low as 0.03 mg/kg/day.
DenBesten (1994) described the limitations of using enamel fluorosis as a biomarker of exposure: enamel fluorosis is useful only for children less than about 7 years old when the exposure occurred; the incidence and degree of fluorosis vary with the timing, duration, and concentration; and there appear to be variations in individual response. Selwitz (1994), summarizing a workshop on the assessment of fluoride accumulation, also indicated that variability in response (incidence and severity of enamel fluorosis) to fluoride exposure may result from physiological differences among individuals and that enamel fluorosis is not an adequate biomarker for fluoride accumulation or potentially adverse health effects beyond the period of tooth formation. Selwitz (1994) did suggest that enamel fluorosis could be used as a biomarker of fluoride exposure in young children within a community over time.

Skeletal fluorosis (see also Chapter 5) is characterized by increased bone mass, increased radiographic density of the bones, and a range of skeletal and joint symptoms; preclinical skeletal fluorosis is associated with fluoride concentrations of 3,500-5,500 ppm in bone ash and clinical stages I, II, and III with concentrations of 6,000-7,000, 7,500-9,000, and >8,400, respectively (PHS 1991), although other sources indicate lower concentrations of bone fluoride in some cases of skeletal fluorosis (see Chapter 5). According to the Institute of Medicine, “Most epidemiological research has indicated that an intake of at least 10 mg/day [of fluoride] for 10 or more years is needed to produce clinical signs of the milder forms of [skeletal fluorosis]” (IOM 1997). However, the National Research Council (NRC 1993) indicated that crippling (as opposed to mild) skeletal fluorosis “might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years.” A previous NRC report (NRC 1977) stated that a retention of 2 mg of fluoride per day (corresponding approximately to a daily intake of 4-5 mg) “would mean that an average individual would experience skeletal fluorosis after 40 yr, based on an accumulation of 10,000 ppm fluoride in bone ash.” Studies in other countries indicate that skeletal fluorosis might be in part a marker of susceptibility as well as exposure, with factors such as dietary calcium deficiency involved in addition to fluoride intake (Pettifor et al. 1989; Teotia et al. 1998).

Hodge and Smith (1965) summarized a number of studies of skeletal fluorosis, including two that indicated affected individuals in the United States with water supplies containing fluoride at 4.8 or 8 mg/L. They also stated categorically that “crippling fluorosis has never been seen in the United States.” The individuals with endemic fluorosis at 4.8 mg/L are referred to elsewhere as having “radiographic osteosclerosis, but no evidence of skeletal fluorosis” (PHS 1991). In combination with high fluid intake and large amounts of tea, “the lowest drinking-water concentration of fluoride
associated with symptomatic skeletal fluorosis that has been reported to date is 3 ppm, outside of countries such as India” (NRC 1977).

Both the PHS (1991) and the NRC (1993) indicated that only five cases of crippling skeletal fluorosis have been reported in the literature in the United States (including one case in a recent immigrant from an area with fluoride in the drinking water at 3.9 mg/L) (PHS 1991). These individuals were said to have water supplies ranging from 3.9 to 8.0 mg/L (water fluoride content given for one of the individuals is actually less than 3.9 mg/L) (PHS 1991). Two of the individuals had intakes of up to 6 L/day of water containing fluoride at 2.4-3.5 or 4.0-7.8 mg/L (PHS 1991; NRC 1993); this corresponds to fluoride intakes of up to 14.4-21 or 24-47 mg/day.

Several cases of skeletal fluorosis reported in the United States are summarized in Table 2-17. These reports indicate that a fluoride concentration of 7-8 mg/L for 7 years is sufficient to bring about skeletal fluorosis (Felsenfeld and Roberts 1991), but skeletal fluorosis may occur at much lower fluoride concentrations in cases of renal insufficiency (Juncos and Donadio 1972; Johnson et al. 1979). People who consume instant tea are at increased risk of developing skeletal fluorosis, especially if they drink large volumes, use extra-strength preparations, or use fluoridated or fluoride-contaminated water (Whyte et al. 2005).

In summary, selecting appropriate biomarkers for a given fluoride study depends on a number of factors, as listed above. A major consideration is the time period of interest for the study (e.g., current or recent exposures versus exposures in childhood versus cumulative exposures) and whether the intent is to demonstrate differences among groups or to characterize exposures of specific individuals. Many of the areas for further research identified by a 1994 workshop (Whitford et al. 1994) are still relevant for improving the assessment of fluoride exposures.

**FINDINGS**

Table 2-18 summarizes various published perspectives on the significance of given concentrations of fluoride exposure. Historically, a daily intake of 4-5 mg by an adult (0.057-0.071 mg/kg for a 70-kg adult) was considered a “health hazard” (McClure et al. 1945, cited by Singer et al. 1985). However, the Institute of Medicine (IOM 1997) now lists 10 mg/day as a “tolerable upper intake” for children > 8 years old and adults, although that intake has also been associated with the possibility of mild (IOM 1997) or even crippling (NRC 1993) skeletal fluorosis.

The recommended optimal fluoride intake for children to maximize caries prevention and minimize the occurrence of enamel fluorosis is often stated as being 0.05-0.07 mg/kg/day (Levy 1994; Heller et al. 1999, 2000). Burt (1992) attempted to track down the origin of the estimate of 0.05-0.07
<table>
<thead>
<tr>
<th>Study Subjects</th>
<th>Exposure Conditions</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 18-year-old boy, 57.4 kg</td>
<td>(a) “high” intake of well water containing fluoride at 2.6 mg/L since early childhood; current intake, 7.6 L/day (0.34 mg/kg/day)</td>
<td>Enamel fluorosis and roentgenographic bone changes consistent with “systemic fluorosis,” attributed to the combination of renal insufficiency and polydipsia (the latter resulting from the renal disease); reported by the Mayo Clinic</td>
<td>Juncos and Donadio 1972</td>
</tr>
<tr>
<td>(b) 17-year-old girl, 45.65 kg</td>
<td>(b) “high” intake of water containing fluoride at 1.7 mg/L since infancy; current intake, 4 L/day (0.15 mg/kg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six renal patients seen at the Mayo Clinic over a several year period (includes the two patients reported by Juncos and Donadio)</td>
<td>Drinking water with 1.7-3 mg/L fluoride; water consumption not stated, but urine volumes of “most” of the patients exceeded 3 L/day</td>
<td>Fluoride “may have been the cause of detectable clinical and roentgenographic effects” Five of the patients had renal disease of at least 15 years duration before skeletal symptoms developed</td>
<td>Johnson et al. 1979</td>
</tr>
<tr>
<td>54-year-old woman in Oklahoma</td>
<td>Well water with fluoride concentration of 7.3-8.2 mg/L (382-429 µmol/L); duration of residence at that location, 7 years; prior to that she had used municipal water at less than 2 mg/L fluoride; water consumption not reported, but considered likely to be “increased” due to hot summers</td>
<td>Osteosclerosis, elevated serum alkaline phosphatase, stiffness of knees and hips Renal insufficiency was not a factor</td>
<td>Felsenfeld and Roberts 1991</td>
</tr>
<tr>
<td>52-year-old woman in Missouri</td>
<td>Daily consumption of 1-2 gallons (3.8-7.6 L) per day of double-strength instant tea made with unfiltered well water (2.8 mg/L fluoride in the well water) for close to 10 years; estimated fluoride intake of 37-74 mg/day (11-22 mg/day from well water and 26-52 mg/day from tea)</td>
<td>Osteosclerosis, increased bone mineral density, bone and joint pains Intake of fluoride from well water alone was considered sufficient to cause mild skeletal fluorosis No mention of any renal disease</td>
<td>Whyte et al. 2005</td>
</tr>
</tbody>
</table>
# TABLE 2-18  Summary of Current and Historical Perspectives on Fluoride Exposure

<table>
<thead>
<tr>
<th>Exposure, mg/kg/day</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0014</td>
<td>“Adequate intake” for children &lt; 6 months old (0.01 mg/day)</td>
<td>IOM 1997; ADA 2005</td>
</tr>
<tr>
<td>0.01-0.04</td>
<td>Average daily dietary fluoride intake for children 0-2 years old residing in nonfluoridated areas (&lt; 0.4 mg/L)</td>
<td>IOM 1997&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.017-0.031</td>
<td>Average daily intake by adults in a fluoridated area (1.2-2.2 mg/day)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NRC 1993</td>
</tr>
<tr>
<td>0.017-0.054</td>
<td>Lower end of “safe and adequate daily dietary intake” for children 0-10 years (0.1-1.5 mg/day)</td>
<td>NRC 1989b</td>
</tr>
<tr>
<td>0.019-0.033</td>
<td>Lower end of “safe and adequate daily dietary intake” for children ≥ 10 years and adults (1.5 mg/day)</td>
<td>NRC 1989b</td>
</tr>
<tr>
<td>0.02-0.10</td>
<td>Average daily dietary fluoride intake for children 1-9 years residing in fluoridated areas (0.7-1.1 mg/L)</td>
<td>McClure 1943&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.038-0.069</td>
<td>Upper end of “safe and adequate daily dietary intake” for children ≥ 10 years and adults (2.5-4.0 mg/day)</td>
<td>NRC 1989b</td>
</tr>
<tr>
<td>0.04-0.07</td>
<td>Average daily intake by children in a fluoridated area</td>
<td>NRC 1993</td>
</tr>
<tr>
<td>0.05</td>
<td>“Adequate intake” for all ages above 6 months old&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IOM 1997; ADA 2005</td>
</tr>
<tr>
<td>0.05</td>
<td>ATSDR’s minimal risk level&lt;sup&gt;e&lt;/sup&gt; (chronic duration, based on increased rate of bone fractures)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>ATSDR 2003</td>
</tr>
<tr>
<td>0.05-0.13</td>
<td>Average daily dietary fluoride intake for children 0-2 years old residing in fluoridated areas (0.7-1.1 mg/L)</td>
<td>IOM 1997&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.05-0.07</td>
<td>“Optimal” intake to maximize caries prevention and minimize the occurrence of enamel fluorosis</td>
<td>Levy 1994; Heller et al. 1999, 2000</td>
</tr>
<tr>
<td>0.05-0.07</td>
<td>“Useful upper limit for fluoride intake in children”</td>
<td>Burt 1992</td>
</tr>
<tr>
<td>0.05-0.071</td>
<td>“Health hazard” for adults (4-5 mg/day)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>McClure et al. 1945</td>
</tr>
<tr>
<td>0.057</td>
<td>EPA’s SMCL (2 mg/L; adult intake)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>40CFR 143.3[2001]</td>
</tr>
<tr>
<td>0.06</td>
<td>EPA’s reference dose&lt;sup&gt;e&lt;/sup&gt; (based on protection of children from objectionable enamel fluorosis)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>EPA 1989</td>
</tr>
<tr>
<td>0.083-0.13</td>
<td>Upper end of “safe and adequate daily dietary intake” for children 0-10 years old&lt;sup&gt;d&lt;/sup&gt; (0.5-2.5 mg/day)</td>
<td>NRC 1989b</td>
</tr>
<tr>
<td>0.10</td>
<td>“Tolerable upper intake”&lt;sup&gt;n&lt;/sup&gt; for ages 0-8 (0.7-2.2 mg/day)</td>
<td>IOM 1997; ADA 2005</td>
</tr>
<tr>
<td>0.10</td>
<td>EPA’s SMCL (2 mg/L; child intake)&lt;sup&gt;m&lt;/sup&gt;</td>
<td>40CFR 143.3 [2001]</td>
</tr>
<tr>
<td>0.11</td>
<td>EPA’s MCLG and MCL (4 mg/L; adult intake)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>40CFR 141.62(b)[2001]</td>
</tr>
<tr>
<td>0.13-0.18</td>
<td>“Tolerable upper intake”&lt;sup&gt;o&lt;/sup&gt; for ages ≥ 14 (10 mg/day)</td>
<td>IOM 1997; ADA 2005</td>
</tr>
<tr>
<td>0.2</td>
<td>EPA’s MCLG and MCL (4 mg/L; child intake)&lt;sup&gt;p&lt;/sup&gt;</td>
<td>40CFR 141.62(b)[2001]</td>
</tr>
</tbody>
</table>

*continued*
mg/kg/day as an optimum intake of fluoride but was unable to find it. He interpreted the available evidence as suggesting that 0.05-0.07 mg/kg/day (from all sources) “remains a useful upper limit for fluoride intake in children” (see also NRC 1993).

Table 2-18 Continued

<table>
<thead>
<tr>
<th>Exposure, mg/kg/day</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>“Tolerable upper intake”(^o) for ages 9-13(^a) (10 mg/day)</td>
<td>IOM 1997; ADA 2005</td>
</tr>
</tbody>
</table>

\(^a\)Based on intakes and average body weights listed by IOM (1997) and ADA (2005); see Table B-17 in Appendix B.
\(^b\)Summaries of papers published between 1979 and 1988 (IOM 1997).
\(^c\)Based on a 70-kg adult.
\(^d\)Based on intakes and median weights listed by NRC (1989b); see Table B-16 in Appendix B.
\(^e\)Summarized by IOM (1997).
\(^f\)Range, 0.045-0.056 mg/kg/day.
\(^g\)A minimal risk level (MRL) is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure (ATSDR 2003).
\(^h\)The ATSDR (2003) states that an intermediate-duration MRL derived from a study of thyroid effects in rats would have been lower (more protective) than the chronic-duration MRL of 0.05, but the value of that MRL is not given.
\(^i\)Based on intake of 2 L/day by a 70-kg adult of water containing fluoride at 2 mg/L.
\(^j\)Reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (EPA 1989).
\(^k\)Based on a fluoride concentration of 1 mg/L in drinking water; the RfD for fluoride contains no uncertainty factor or modifying factor, although RfDs for other substances contain uncertainty factors to account for things such as variability within the human population (EPA 2003b).
\(^l\)Based on moderate enamel fluorosis (IOM 1997).
\(^m\)Based on intake of 1 L/day by a 20-kg child of water containing fluoride at 2 mg/L.
\(^n\)Based on intake of 1 L/day by a 20-kg child of water containing fluoride at 4 mg/L.
\(^o\)Based on skeletal fluorosis for adults and children ≥ age 9 (IOM 1997).
\(^p\)Based on intake of 1 L/day by a 20-kg child of water containing fluoride at 4 mg/L.

Figure 2-8 shows the average intake of fluoride from all sources estimated in this report (Table 2-11), with 1 mg/L in drinking water; Figure 2-9 shows the average intake of fluoride from drinking water alone (Table 2-10), given a fluoride concentration at the MCLG/MCL (4 mg/L). For comparison purposes, an intake of 0.05-0.07 mg/kg/day is indicated on the graphs.

Based on EPA’s estimates of community water consumption by consumers with an average intake (EPA 2000a), if that water is fluoridated, children
less than 6 months old have an intake at or above 0.05-0.07 mg/kg/day (see Appendix B, Table B-10). Children from 6 months to 1 year old have similar intakes if their water is fluoridated at 1 or 1.2 mg/L. No other age groups have that intake at ordinary fluoride concentrations; all age groups reach or exceed that intake with water at 4 mg/L. For individuals with higher-than-average intake of community water, intakes for the youngest children (<1 year) might exceed 0.05-0.07 mg/kg/day at all concentrations of water fluoridation (see Appendix B, Tables B-11, B-12, and B-13); for fluoride concentrations corresponding to the SMCL (2 mg/L) or MCL (4 mg/L), an intake of 0.05-0.07 mg/kg/day is reached or exceeded by all age groups. Note that the estimates in Appendix B include only the fluoride contribution from
FIGURE 2-9 Estimated average intake of fluoride from drinking water alone, based on a fluoride concentration of 4 mg/L (MCLGl/MCL; based on Table 2-10). Horizontal lines indicate an intake of 0.05-0.07 mg/kg/day.

community water (drinking water, plus beverages and foods prepared with community water at home or in local eating establishments); if contributions from food, tea, commercial beverages, toothpastes, and other sources are added, total intakes by individuals will increase accordingly.

Estimates of total exposure (typical or average) shown in Table 2-11 indicate that all children through age 12 who take fluoride supplements (assuming low water fluoride) will reach or exceed 0.05-0.07 mg/kg/day. For children not on supplements, nonnursing infants with fluoride in tap water at ≥0.5 mg/L will exceed 0.05-0.07 mg/kg/day for typical exposures. Also, children through 5 years old (≥0.5 mg/L in tap water), children 6-12 years old (≥2 mg/L in tap water), and teenagers and adults (≥4 mg/L in tap water) will exceed 0.05-0.07 mg/kg/day with typical or average fluoride exposures in terms of water consumption and toothpaste ingestion.
A number of researchers have pointed out both the importance of evaluating individual fluoride intake from all sources and the difficulties associated with doing so, given the variability of fluoride content in various foods and beverages and the variability of individual intakes of the specific items (Clovis and Hargreaves 1988; Nowak and Nowak 1989; Chan et al. 1990; Stannard et al. 1990, 1991; Weinberger 1991; Toumba et al. 1994; Duperon et al. 1995; Van Winkle et al. 1995; Chan and Koh 1996; Kiritsy et al. 1996; Warren et al. 1996; Heilman et al. 1997, 1999; Heller et al. 1999; Levy and Guha-Chowdhury 1999; Lalumandier and Ayers 2000). However, as shown in Figure 2-1, for typical individuals, the single most important contributor to fluoride exposures (approaching 50% or more) is fluoridated water and other beverages and foods prepared or manufactured with fluoridated water.

**RECOMMENDATIONS**

- Fluoride should be included in nationwide biomonitoring surveys and nutritional studies (e.g., CDC’s National Health and Nutrition Examination Survey and affiliated studies). In particular, analysis of fluoride in blood and urine samples taken in these surveys would be valuable.
- National data on fluoridation (e.g., CDC 1993) should be updated on a regular basis.
- Probabilistic analysis should be performed for the uncertainty in estimates of individual and group exposures and for population distributions of exposure (e.g., variability with respect to long-term water consumption). This would permit estimation of the number of people exposed at various concentrations, identification of population subgroups at unusual risk for high exposures, identification or confirmation of those fluoride sources with the greatest impact on individual or population exposures, and identification or characterization of fluoride sources that are significant contributors to total exposure for certain population subgroups.
- To assist in estimating individual fluoride exposure from ingestion, manufacturers and producers should provide information on the fluoride content of commercial foods and beverages.
- To permit better characterization of current exposures from airborne fluorides, ambient concentrations of airborne hydrogen fluoride and particulates should be reported on national and regional scales, especially for areas of known air pollution or known sources of airborne fluorides. Additional information on fluoride concentrations in soils in residential and recreational areas near industrial fluoride sources also should be obtained.
- Additional studies on the relationship between individual fluoride exposures and measurements of fluoride in tissues (especially bone and nails) and bodily fluids (especially serum and urine) should be conducted. Such
studies should determine both absolute intakes (mg/day) and body-weight normalized intakes (mg/kg/day).

- Assumptions about the influence of environmental factors, particularly temperature, on water consumption should be reevaluated in light of current lifestyle practices (e.g., greater availability of air conditioning, participation in indoor sports).

- Better characterization of exposure to fluoride is needed in epidemiology studies investigating potential effects. Important exposure aspects of such studies would include the following:
  - collecting data on general dietary status and dietary factors that could influence exposure or effects, such as calcium, iodine, and aluminum intakes
  - characterizing and grouping individuals by estimated (total) exposure, rather than by source of exposure, location of residence, fluoride concentration in drinking water, or other surrogates
  - reporting intakes or exposures with and without normalization for body weight (e.g., mg/day and mg/kg/day)
  - addressing uncertainties associated with exposure, including uncertainties in measurements of fluoride concentrations in bodily fluids and tissues
  - reporting data in terms of individual correlations between intake and effect, differences in subgroups, and differences in percentages of individuals showing an effect and not just differences in group or population means.

- Further analysis should be done of the concentrations of fluoride and various fluoride species or complexes (especially fluorosilicates and aluminofluorides) present in tap water, using a range of water samples (e.g., of different hardness and mineral content). Research also should include characterizing any changes in speciation that occur when tap water is used for various purposes—for example, to make acidic beverages.
  - The possibility of biological effects of SiF$_6^{2-}$, as opposed to free fluoride ion, should be examined.
  - The biological effects of aluminofluoride complexes should be researched further, including the conditions (exposure conditions and physiological conditions) under which the complexes can be expected to occur and to have biological effects.
Pharmacokinetics of Fluoride

This chapter updates pharmacokinetic information on fluoride developed since the earlier National Research Council review (NRC 1993). Particular attention is given to several potentially important issues for evaluation of the U.S. Environmental Protection Agency (EPA) maximum-contaminant-level goal (MCLG), including the accumulation of fluoride in bone, pharmacokinetic modeling, cross-species extrapolation, and susceptible populations. Consideration of biomarkers is provided in Chapter 2.

OVERVIEW OF FLUORIDE CHEMISTRY, UNITS, AND MEASUREMENT

Fluoride is the ionic form of fluorine, the most electronegative element. Water in the United States is typically fluoridated with fluorosilicates or sodium fluoride. In water at approximately neutral pH, fluorosilicates appear to entirely dissociate, producing fluoride ion, hydrofluoric acid (HF), and silicic acid (Si(OH)4). Fluoride reversibly forms HF in water. It also complexes with aluminum. See Chapter 2 for additional discussion of fluorosilicates and aluminum fluoride complexes.

Inorganic fluoride takes two primary forms in body fluids: fluoride ion and HF. Organofluorine compounds, and their potential relationship to inorganic fluoride, are discussed in Chapter 2 and later in this chapter.

A number of different units are commonly used to measure fluoride concentrations in water and biological samples (Table 3-1). Because the atomic weight of fluorine is 19, 1 µmol/L is equal to 0.019 milligrams per liter (mg/L). Bone ash is typically about 56% of wet bone by weight (Rao...
et al. 1995), so 1,000 milligrams per kilogram (mg/kg) of fluoride in bone ash is equivalent to about 560 mg/kg wet weight.

Fluoride concentrations in body fluids typically are measured with a fluoride-specific electrode, an instrument that cannot reliably measure concentrations below about 0.019 mg/L and tends to overpredict at lower concentrations. As many people living in areas with artificially fluoridated water have plasma concentrations in this range, studies that rely on fluoride electrodes alone might tend to overpredict concentrations in plasma and body fluids. The hexamethyldisiloxane diffusion method provides a way around this problem by concentrating the fluoride in samples before analysis (reviewed by Whitford 1996).

**SHORT REVIEW OF FLUORIDE PHARMACOKINETICS: ABSORPTION, DISTRIBUTION, AND ELIMINATION**

A comprehensive review of fluoride pharmacokinetics is provided by Whitford (1996), and this section presents a brief overview of that information. The pharmacokinetics of fluoride are primarily governed by pH and storage in bone. HF diffuses across cell membranes far more easily than fluoride ion. Because HF is a weak acid with a pKa of 3.4, more of the fluoride is in the form of HF when pH is lower. Consequently, pH—and factors that affect it—play an important role in the absorption, distribution, and excretion of fluoride. Fluoride is readily incorporated into calcified tissues, such as bone and teeth, substituting for hydroxyls in hydroxyapatite crystals. Fluoride exchanges between body fluids and bone, both at the surface layer of bone (a short-term process) and in areas undergoing bone remodeling (a longer-term process). Most of the fluoride in the body, about 99%, is contained in bone.

Fluoride is well absorbed in the alimentary tract, typically 70% to 90%. For sodium fluoride and other very soluble forms, nearly 100% is absorbed. Fluoride absorption is reduced by increased stomach pH and increased concentrations of calcium, magnesium, and aluminum. At high concentrations, those metals form relatively insoluble fluoride salts. A recent study comparing hard and soft water found little difference in fluoride bioavailability in healthy young volunteers (Maguire et al. 2004). Fluoride

<table>
<thead>
<tr>
<th>Medium</th>
<th>Unit</th>
<th>Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1 ppm</td>
<td>1 mg/L</td>
</tr>
<tr>
<td>Plasma</td>
<td>1 µmol/L</td>
<td>0.019 mg/L</td>
</tr>
<tr>
<td>Bone ash</td>
<td>1 ppm</td>
<td>1 mg/kg</td>
</tr>
</tbody>
</table>

**TABLE 3-1 Commonly Used Units for Measuring Fluoride**
Fluoride concentrations in plasma, extracellular fluid, and intracellular fluid are in approximate equilibrium. The concentrations in the water of most tissues are thought to be 40% to 90% of plasma concentrations, but there are several important exceptions. Tissue fluid/plasma (T/P) ratios exceed one for the kidney because of high concentrations in the renal tubules. T/P ratios can exceed one in tissues with calcium deposits, such as the placenta near the end of pregnancy. The pineal gland, a calcifying organ that lies near the center of the brain but outside the blood-brain barrier, has been found to accumulate fluoride (Luke 2001). Fluoride concentrations in adipose tissue and brain are generally thought to be about 20% of plasma or less (Whitford 1996). The blood-brain barrier is thought to reduce fluoride transfer, at least in short-term experiments (Whitford 1996). It is possible that brain T/P ratios are higher for exposure before development of the blood-brain barrier.

Most tissue measurements are based on short-term exposures of healthy adult animals. Similar T/P ratios have been found for liver and kidney in some chronic animal experiments (Dunipace et al. 1995), but not all organs have been examined. The literature contains some unexplained exceptions to these T/P generalizations (Mullenix et al. 1995; Inkielewicz and Krechniak 2003). Mullenix et al. (1995) reported atypically high, dose-dependent T/P ratios for the rat brain: more than 20 for control animals and about 3 for animals exposed to fluoride at 125 mg/L in drinking water for 20 weeks. Because these T/P ratios for brain are much higher than earlier results, Whitford (1996) speculated that the results of Mullenix et al. were due to analytical error. Additional measurements of fluoride tissue concentrations after chronic dosing are needed.

Fluoride is cleared from plasma through two primary mechanisms: uptake by bone and excretion in urine. Plasma clearance by the two routes is approximately equal in healthy adult humans. (Plasma clearance is the volume of plasma from which fluoride is removed per unit time. The rate of removal equals the clearance times the plasma fluoride concentration. Clearances are additive.) The relative clearance by bone is larger in young animals and children because of their growing skeletal systems. “In contrast to the compact nature of mature bone, the crystallites of developing bone are small in size, large in number and heavily hydrated. Thus, they afford a relatively enormous surface area for reactions involving fluoride” (Whitford 1996, p. 94). Experimental work in growing dogs demonstrates that extrarenal clearance, almost entirely uptake by bone, is inversely related to age. Renal clearance depends on pH and glomerular filtration rate. At low pH, more HF is formed, promoting reabsorption. Excretion of previously absorbed fluoride from the body is almost entirely via urine. Fluoride not absorbed
fluoride is found in feces. High concentrations of calcium in contents of the gastrointestinal tract can cause net excretion of fluoride.

Fluoride is rapidly absorbed from the gastrointestinal tract, with a half-life of about 30 minutes. After a single dose, plasma concentrations rise to a peak and then fall as the fluoride is cleared by the renal system and bone, decreasing back to (short-term) baseline with a half-life of several hours. Fluoride concentrations in plasma are not homeostatically controlled (Whitford 1996). Chronic dosing leads to accumulation in bone and plasma (although it might not always be detectable in plasma.) Subsequent decreases in exposure cause fluoride to move back out of bone into body fluids, becoming subject to the same kinetics as newly absorbed fluoride. A study of Swiss aluminum workers found that fluoride bone concentrations decreased by 50% after 20 years. The average bone ash concentration in the workers was about 6,400 mg/kg at the end of exposure, estimated via regression (Baud et al. 1978). The bone concentration found in these workers is similar to that found in long-term consumers of drinking water containing fluoride in the range of 2-4 mg/L (discussed later in this chapter). Twenty years might not represent a true half-life. Recent pharmacokinetic models (see below) are nonlinear, suggesting that elimination rates might be concentration dependent.

**PHARMACOKINETIC MODELS**

Pharmacokinetic models can be useful for integrating research results and making predictions. Two important fluoride models have been published since the 1993 NRC review. Turner et al. (1993) modeled bone concentrations in healthy adult humans. They assumed a nonlinear function relating the concentrations of fluoride in newly formed bone to plasma/extracellular fluids. The relationship is close to linear until bone ash concentrations reach about 10,000 mg/kg; above that concentration the curve levels off. (Based on the chemical structure of fluorapatite, Ca$_{10}$(PO$_4$)$_6$F$_2$, the theoretical limit on bone fluoride concentration is 37,700 mg/kg.) The model was relatively successful at predicting fluoride bone concentrations due to chronic exposure compared with experimental data—for example, the human bone measurements of Zipkin et al. (1958). Bone fluoride concentrations were predicted to increase approximately linearly as a function of water concentration, at least up to 4 mg/L. The most sophisticated model to date (Rao et al. 1995) extended this work with a physiologically based pharmacokinetic (PBPK) model. Among other features, it models change in body weight, plasma clearance, and bone uptake as a function of sex and age, allowing predictions for lifetime exposures. It can model both rats and humans, making it useful for comparing these species. Predicted bone concentrations were comparable with data from several studies of humans,
including the study by Zipkin et al. (1958), and two rat carcinogenicity studies (Maurer et al. 1990; Bucher et al. 1991). Both models predicted increasing fluoride concentrations in bone with length of chronic exposure. None of these studies presented results for plasma.

Both models also performed well in predicting bone concentrations of fluoride resulting from osteoporosis treatment, involving about 25 mg of fluoride per day for up to 6 years. This suggests that the models can adequately predict the results of both long-term lower exposures (drinking water) and shorter-term, higher exposures (treatment regimes) by changing exposure assumptions.

The PBPK model of Rao et al. (1995) could be used in several ways, including (1) predicting bone concentrations in people after lifetime exposures to assumed water concentrations or other exposure scenarios, and (2) comparing plasma and bone fluoride concentrations in rats and humans with the same exposure. The Rao model is quite complicated and relies on several numerical functions not provided in the paper. The Turner model is more limited in scope, unable to compare species or take sex- and age-related effects into account, but it is much simpler. Not enough detail on either model was available to replicate them nor was the committee able to obtain operational versions of the models.

**FLUORIDE CONCENTRATIONS IN HUMAN BONE VERSUS WATER CONCENTRATION**

Remarkably few data are available for studying the association between fluoride in human bone and low-dose chronic exposure via drinking water. Although there are a number of cross-sectional studies comparing bone concentrations with water concentrations, very few contain estimates of length of exposure. Most studies are autopsies, as bone samples can be difficult to obtain from healthy living subjects. Among studies examining exposure to fluoride at 4 mg/L, Zipkin et al. (1958) provided the only data set that included exposure durations. The results of that study were also modeled by Turner et al. (1993) and Rao et al. (1995). Sixty-three of the 69 subjects, aged 26 to 90, died suddenly, primarily due to trauma, cardiovascular disease, and cerebrovascular causes; three had renal disease. The authors recorded concentrations of fluoride in drinking water and bone as well as sex, age, and years of residence. Compared with today, many other sources of fluoride exposure were uncommon or did not exist. The average residence time for the whole study was 31 years, 34 years for the 2.6-mg/L group and 21 years for the 4-mg/L group. Exposure took place for most people as adults. No estimates of water consumption are provided: water concentration serves as an ecologic measure of exposure.

Table 3-2 summarizes data on fluoride content of the iliac crest, the
bone modeled by Turner et al. and Rao et al. Zipkin et al. concluded that average bone fluoride concentrations were linearly related to water concentration. (As discussed in Appendix C, this analysis is fully ecologic). The committee regressed individual-level bone concentrations versus water concentrations (a group measure of exposure) and individual-level covariates such as age. (This analysis is partially ecologic.) Figure 3-1 plots bone versus water concentrations and the result of simple regression with no covariates. (Note the apparent heteroscedasticity.) The model was improved

\[
y = 517 + 1,549x; \ (r^2 = 0.66); \ \text{slope} = 1,549 \ (95\% \ \text{confidence interval [CI]} = 1,227, 1,872).
\]

### TABLE 3-2 Fluoride in Bone Due to Chronic Water Exposure\(^a\)

<table>
<thead>
<tr>
<th>Water Concentration, mg/L</th>
<th>Average Iliac Crest Concentration, mg/kg Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>665 ± 224 (n = 17)</td>
</tr>
<tr>
<td>1</td>
<td>2,249 ± 506 (n = 4)</td>
</tr>
<tr>
<td>2.6</td>
<td>4,496 ± 2,015 (n = 25)</td>
</tr>
<tr>
<td>4</td>
<td>6,870 ± 1,629 (n = 4)</td>
</tr>
<tr>
<td>Total</td>
<td>3,203 (n = 50)</td>
</tr>
</tbody>
</table>

\(^a\)Fifty-three subjects had data for the iliac crest; 3 from the 0.2 and 0.3 mg/L groups are omitted because they were also exposed to fluoridated water for 2 to 4 years.


FIGURE 3-1 Iliac crest data from Zipkin et al. (1958). Crude regression results: \(y = 517 + 1,549x; \ (r^2 = 0.66); \ \text{slope} = 1,549 \ (95\% \ \text{confidence interval [CI]} = 1,227, 1,872).
by including residence years and sex; age had little additional impact and was omitted in the final model (Table 3-3).

Several cross-sectional studies have found an association between fluoride bone concentrations and age (Jackson and Weidmann 1958; Kuo and Stamm 1974; Parkins et al. 1974; Charen et al. 1979; Alhava et al. 1980; Eble et al. 1992; Richards et al. 1994; Torra et al. 1998). Jackson and Weidmann (1958) were unusual in finding a leveling off at an older age. But most studies did not have information on length of exposure, a variable often correlated with age (R = 0.41 in the Zipkin data set). Because of the potential for rapid fluoride uptake by bones during childhood, the committee modeled exposure before puberty with an indicator variable, but this added little to the model. Very few data are available on bone fluoride concentrations in children. Most studies do not distinguish between trabecular and cortical bone, although the former have higher fluoride concentrations (Eble et al. 1992).

The model in Table 3-3 indicates that fluoride bone concentrations increased with fluoride water concentrations and residence time; females tended to have higher concentrations than males. These results need to be interpreted with caution. Some subjects had renal disease, which can sometimes increase fluoride concentrations (see discussion below), potentially reducing the generalizability of the results to a healthier population. The committee’s analysis is partially ecologic (Appendix C). However, the Turner and Rao pharmacokinetic models also predict that fluoride bone concentrations increase with water concentration and duration of chronic exposure.

What bone fluoride concentration occurs after 70 years of exposure to water at 4 mg/L? The multiple regression model predicts about 8,100 mg/kg ash for females, within the range of the data set used to construct the model but near its maximum. Few people studied by Zipkin et al. were exposed for 70 years and only four were exposed at 4 mg/L. Fluoride is taken up by bone more rapidly during growth than in adulthood. This phenomenon, not addressed by the regression model, could cause the model to underpredict. Only the model of Rao et al. was constructed to examine lifetime exposure. Assuming 70 years of exposure at 4 mg/L in water, Rao et al. predicted fluoride concentrations of 10,000 to 12,000 mg/kg in bone ash for females. Even

<table>
<thead>
<tr>
<th>TABLE 3-3 Multiple Regression Results for Zipkin Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
</tr>
<tr>
<td>Intercept</td>
</tr>
<tr>
<td>Water fluoride</td>
</tr>
<tr>
<td>Residence, years</td>
</tr>
<tr>
<td>Sex (M = 0)</td>
</tr>
</tbody>
</table>
higher values would be predicted if other sources of fluoride exposure were included. This prediction lies beyond the range of the human data used to check the model, but it represents the current best estimate. In making this prediction, the authors appear to have assumed consumption of 1 L of water per day up to age 10 and 2 L/day thereafter. Higher water consumption rates (e.g., 5 L/day) would further increase bone concentrations of fluoride but by less than fivefold because of the nonlinear kinetics.

Unfortunately, Rao et al. did not publish predictions for 2 mg/L. The regression model of Table 3-3 predicts about 5,000 mg/kg ash for females after 70 years of exposure. This value exceeds the mean value (4,500 mg/kg) observed at 2.6 mg/L in the Zipkin study, primarily because of the assumed longer time of residence. As this estimate is based on regression modeling of the Zipkin data, it may underestimate predictions based on pharmacokinetic modeling or additional sources of exposure. The committee located only a few other studies that measured bone fluoride at similar water concentrations. A British study found bone concentrations of about 5,700 mg/kg ash in people chronically exposed to water with fluoride at 1.9 mg/L; these people are also thought to be exposed to fluoride in tea (Jackson and Weidmann 1958; see Turner et al. 1993 for unit conversions). In an area of rural Finland with fluoride in drinking water exceeding 1.5 mg/L, the average bone concentrations from 57 autopsies were 3,490 mg/kg ash in females and 2,830 mg/kg ash in males (Arnala et al. 1985). Most had lived their whole lives in the same place, most were over 50, and 7 had impaired renal function. For 16, fluoride concentrations were measured in the water sources (2.6 ± 1.4 mg/L); bone concentrations were 4,910 ± 2,250 mg/kg ash. In a later study of the same area of Finland, the mean bone concentration in 18 hip fracture patients was 3,720 ± 2,390 mg/kg, assumed to be ash (Arnala et al. 1986). The mean age was 79, 14 were female, 3 had diabetes, and 1 had elevated serum creatinine; residence time was not specified. For people exposed to fluoride at 2 mg/L in drinking water for a lifetime, the committee concludes that average bone concentration can be expected to be in the range of 4,000 to 5,000 mg/kg ash. Considerable variation around the average is expected.

**FLUORIDE CONCENTRATIONS IN BONES**

**AFTER CLINICAL STUDIES**

A number of clinical studies measured bone fluoride concentrations after therapeutic treatment (van Kesteren et al. 1982; Boivin et al. 1988; Bayley et al. 1990; Gutteridge et al. 1990; Orcel et al. 1990; Boivin et al. 1993; Søgaard et al. 1994; Lundy et al. 1995). Figure 3-2 summarizes these data, plotting fluoride concentrations in bone ash after treatment versus total exposure from the studies. The weighted least squares (WLS) regression
line weighted points according to the number of participants in each trial (see Appendix C). Note that the two points farthest above the regression line (Bayley et al. 1990; Lundy et al. 1995) were from studies carried out in Toronto and Minnesota, presumably fluoridated areas; most (possibly all) of the other studies were conducted in European countries that do not fluoridate water. The two points farthest below the line delivered fluoride in a form designed to reduce bioavailability (Boivin et al. 1988, Turner et al. 1993). This analysis is ecologic, plotting average bone concentrations versus total exposure. However, analysis of individual-level data in two studies (van Kesteren et al. 1982; Gutteridge et al. 1990) provides similar results.

Because the pharmacokinetics of fluoride are nonlinear, we would not necessarily expect people with the same cumulative exposure to have the same bone fluoride concentrations. Indeed, the model may overpredict bone concentrations for long-term exposure to lower fluoride concentrations via water. Figure 3-2 also shows the average bone ash concentrations measured by Zipkin et al. for fluoride at 4 mg/L plotted against estimated total exposure. The latter was estimated assuming consumption of 1.51 L of water per day (Turner et al. 1993) and 21 years of exposure to fluoride in the 4-mg/L area. (The Zipkin study reported residence time and water concentrations but not water consumption.) While not completely out of range, the bone concentration is lower than expected based on the regression for the clinical data. Analysis of Turner’s pharmacokinetic model (Turner et al. 1993) suggests that short-term (months to years), high-dose exposures

FIGURE 3-2 Bone fluoride concentrations versus total exposure in clinical trials. For comparison, the average bone concentration found by Zipkin et al. (1958) among subjects drinking water with fluoride at 4 mg/L is provided.
may produce higher bone fluoride concentrations than long-term (decades), low-dose exposures. More time means more bone resorption, allowing a greater fraction of the total fluoride dose to be excreted. Additional research on this topic would be useful.

More detailed information on fluoride’s effects on bone cells and bone formation is presented in Chapter 5.

COMPARATIVE PHARMACOKINETICS OF RATS AND HUMANS

Among animal species, fluoride toxicology has been studied most extensively in rats. When extrapolating from rats to humans, it is useful to consider their relative pharmacokinetics. There are at least two ways to do this. Bone, tissue, or plasma concentrations may provide an appropriate biomarker of internal exposure for some effects. Alternatively, one can compare plasma, tissue, and bone concentrations in rats and humans given the same dose.

Our knowledge of the comparative pharmacokinetics of fluoride is primarily limited to short-term studies of a small number of mammals. Using estimates of plasma, renal, and extrarenal fluoride clearances scaled to body weight, Whitford et al. (1991) concluded that dogs were the best pharmacokinetic model for humans, based on studies of healthy young adults. In contrast, renal clearance in rats (age 12 weeks) was more than three times larger than in humans; rat extrarenal clearance was about twice as large (Whitford et al. 1991). Unlike in humans, rat bones do not undergo Haversian remodeling (remodeling along channels within the bone). Fluoride uptake by the bones of adult rats should be minimal (Turner et al. 1995).

Comparisons between species—and within species for different experiments—are complicated by several factors. With chronic exposure, fluoride bone concentrations tend to increase over time. The amount of calcium in the diet affects the amount of fluoride absorbed. The dose of fluoride can depend on the concentration of fluoride in water, water consumption, and the amount of fluoride in the diet. If fluoride concentration is kept constant in water, dose can vary as the animal ages. Species age at different rates, and age affects pharmacokinetics, especially bone development and kidney function.

Evidence suggests that rats require higher chronic exposure than humans to achieve the same plasma and bone fluoride concentrations. It has been suggested that rats might require water concentrations about five times larger than humans to reach the same plasma concentration (Dunipace et al. 1995). For bone, Turner et al. (1992) estimated that “humans incorporate fluoride ~18 times more readily than rats when the rats are on a normal calcium diet.” This comparison was also based on water concentrations. In Appendix D, this issue is briefly reviewed. The factor for plasma is uncertain, in
part because it could change with age or duration of dose. It might be more appropriate to compare exposures than water concentration. Bone comparisons are also uncertain but appear to support a rat-to-human conversion factor for older rats and humans of at least an order of magnitude.

ORGANOFLUORINE COMPOUNDS

Two types of fluorine are found in human plasma: inorganic and organic. Up to now, this chapter has discussed the inorganic form. Remarkably, the amount of organic fluoride in serum is generally greater than the amount of inorganic fluoride (Whitford 1996). Interest in organofluorine compounds has grown tremendously in the last decade. Two compounds (and their salts) dominate recent biological research: perfluorooctanesulfonate (PFOS; \( \text{C}_8\text{F}_{17}\text{SO}_3^- \)) and perfluorooctanoate (PFOA; \( \text{C}_7\text{F}_{15}\text{COO}^- \)). Both are straight-chain compounds with fluorine substituted for aliphatic hydrogens. These compounds are biologically stable with long half-lives, on the order of years, in humans. Relatively little is known about the routes of human exposure. A recent study of American Red Cross adult blood donors found median serum concentrations of 35 µg/L of PFOS and 5 µg/L of PFOA (Olsen et al. 2003).

Defluorination of PFOA has not been detected in rat experiments (Vanden Heuvel et al. 1991; Kudo and Kawashima 2003). Given the stability of PFOA and PFOS, they do not appear to be important sources of inorganic fluoride, although more research is needed, particularly for PFOS. Degradation of other fluorocarbons might produce fluoride ion. Perfluorooctanesulfonyl fluoride (POSF, \( \text{C}_8\text{F}_{17}\text{SO}_2\text{F} \)) is used as a starting material for manufacturing polymers and surfactants. Residual POSF in products “may degrade or metabolize, to an indeterminate degree” to PFOS (Olsen et al. 2004, p. 1600). Certain anesthetics release fluoride ion during use (see Chapter 2).

FACTORS MODIFYING PHARMACOKINETICS AND THEIR IMPLICATIONS FOR POTENTIALLY SUSCEPTIBLE POPULATIONS

Changes in chronic exposure to fluoride will tend to alter plasma and bone fluoride concentrations. A number of factors can modify the pharmacokinetics, providing another way to change fluoride tissue concentrations.

Fluoride clearance tends to increase with urinary pH. One proposed mechanism is decreased reabsorption in the renal tubule, easily crossed by HF and nearly impermeable to fluoride ion. Increasing urinary pH thus tends to decrease fluoride retention. As a result, fluoride retention might be affected by environments or conditions that chronically affect urinary pH,
including diet, drugs, altitude, and certain diseases (e.g., chronic obstructive pulmonary disease) (reviewed by Whitford 1996).

Because of their growing skeleton, infants and children clear relatively larger amounts of fluoride into bones than adults (Ekstrand et al. 1994; Whitford 1999). As discussed earlier, fluoride plasma and bone concentrations tend to increase with age. Although this trend is partly due to accumulation over time, decreased renal clearance and differences in bone resorption (preferential removal of crystals with little or no fluoride in the elderly have been hypothesized to play a role.

Because the kidney is the major route of excretion, increased plasma and bone fluoride concentrations are not surprising in patients with kidney disease. Plasma fluoride concentrations are clearly elevated in patients with severely compromised kidney function, reduced glomerular filtration rates of around 20% of normal, as measured via creatinine clearance or serum creatinine concentrations (Hanhijärvi 1974, 1982; Parsons et al. 1975; Schiff and Binswanger 1980; Waterhouse et al. 1980; Hanhijärvi and Penttilä 1981). Kuo and Stamm (1975) found no association. However, elevated serum concentrations were found in renal patients with normal serum creatinine (Hanhijärvi 1982).

Only a few studies have examined fluoride concentrations in bone in renal patients. Call et al. (1965) found doubled bone fluoride concentrations in five patients with chronic, severe kidney disease. Juncos and Donadio (1972) diagnosed systemic fluorosis (but did not measure bone fluoride concentrations) in two patients with reduced renal function and exposure to drinking water with fluoride at 1.7 and 2.6 mg/L. Four renal patients with severe skeletal changes or bone pain had elevated serum and bone fluoride concentrations; the bone concentrations ranged from about 5,500 to 11,000 mg/kg (Johnson et al. 1979). Fluoride bone concentrations more than doubled in four patients with severe, chronic pyelonephritis (Hefti and Marthaler 1981). Arnala et al. (1985) reported elevated bone concentrations (roughly 50%) in six people with “slightly impaired renal function” from a fluoridated area. Bone fluoride concentrations were significantly increased in dialysis patients compared with normal controls (Cohen-Solal et al. 2002). In rats with surgically induced renal deficiency (80% nephrectomy), glomerular filtration rate decreased by 68%. After 6 months of fluoride treatment, bone fluoride concentrations approximately doubled (Turner et al. 1996).

Hanhijärvi and Penttilä (1981) reported elevated serum fluoride in patients with cardiac failure. Fluoride concentrations were positively related to serum creatinine, although the concentrations of the latter did not indicate renal insufficiency. During cardiac failure, the body tries to maintain blood flow to the heart and brain.

Although some studies report no difference in plasma fluoride concen-
trations between men and women (e.g., Torra et al. 1998), others found greater rates of increase with age in females (Husdan et al. 1976; Hanhijärvi et al. 1981). Enhanced release of fluoride in postmenopausal women is one possible explanation. Similar to our regression results of the Zipkin data, some studies have found a tendency toward elevated bone fluoride concentrations in women (Arnala et al. 1985; Richards et al. 1994). A Finnish study reported that bone fluoride concentrations increased more rapidly with age in women than in men (Alhava et al. 1980). This variability might be due to several factors, including individual differences in water consumption and pharmacokinetics.

In sum, although the data are sparse, severe renal insufficiency appears to increase bone fluoride concentrations, perhaps as much as twofold. The elderly are at increased risk of high bone fluoride concentrations due to accumulation over time; although less clear, decreased renal function and gender may be important.

**FINDINGS**

- Bone fluoride concentrations increase with both magnitude and length of exposure. Empirical data suggest substantial variations in bone fluoride concentrations at any given water concentration.
- On the basis of pharmacokinetic modeling, the current best estimate for bone fluoride concentrations after 70 years of exposure to fluoride at 4 mg/L in water is 10,000 to 12,000 mg/kg in bone ash. Higher values would be predicted for people consuming large amounts of water (>2 L/day) or for those with additional sources of exposure. Less information was available for estimating bone concentrations from lifetime exposure to fluoride in water at 2 mg/L. The committee estimates average bone concentrations of 4,000 to 5,000 mg/kg ash.
- Groups likely to have increased bone fluoride concentrations include the elderly and people with severe renal insufficiency.
- Pharmacokinetics should be taken into account when comparing effects of fluoride in different species. Limited evidence suggests that rats require higher chronic exposures than humans to achieve the same plasma and bone concentrations.

**RESEARCH RECOMMENDATIONS**

- Additional research is needed on fluoride concentrations in human bone as a function of magnitude and duration of exposure, age, gender, and health status. Such studies would be greatly aided by noninvasive means of measuring bone fluoride. As discussed in other chapters of this report, some soft tissue effects may be associated with fluoride exposure. Most measure-
ments of fluoride in soft tissues are based on short-term exposures and some atypically high values have been reported. Thus, more studies are needed on fluoride concentrations in soft tissues (e.g., brain, thyroid, kidney) following chronic exposure.

- Research is needed on fluoride plasma and bone concentrations in people with small to moderate changes in renal function as well as patients with serious renal deficiency. Other potentially sensitive populations should be evaluated, including the elderly, postmenopausal women, and people with altered acid-base balance.
- Improved and readily available pharmacokinetic models should be developed.
- Additional studies comparing pharmacokinetics across species are needed.
- More work is needed on the potential for release of fluoride by the metabolism of organofluorines.
In this chapter, the committee reviews research on the occurrence of enamel fluorosis at different concentrations of fluoride in drinking water, with emphasis on severe enamel fluorosis and water fluoride concentrations at or near the current maximum contaminant level goal (MCLG) of 4 mg/L and the secondary maximum contaminant level (SMCL) of 2 mg/L. Evidence on dental caries in relation to severe enamel fluorosis, aesthetic and psychological effects of enamel fluorosis, and effects of fluoride on dentin fluorosis and delayed tooth eruption is reviewed as well. Evidence on caries prevention at water concentrations below the SMCL of 2 mg/L is not reviewed. Strengths and limitations of study methods, including issues pertaining to diagnosis and measurement, are considered.

ENAMEL FLUOROSIS

Fluoride has a great affinity for the developing enamel because tooth apatite crystals have the capacity to bind and integrate fluoride ion into the crystal lattice (Robinson et al. 1996). Excessive intake of fluoride during enamel development can lead to enamel fluorosis, a condition of the dental hard tissues in which the enamel covering of the teeth fails to crystallize properly, leading to defects that range from barely discernable markings to brown stains and surface pitting. This section provides an overview of the clinical and histopathological manifestations of enamel fluorosis, diagnostic issues, indexes used to characterize the condition, and possible mechanisms.
Clinical and Histological Features

Enamel fluorosis is a mottling of the tooth surface that is attributed to fluoride exposure during tooth formation. The process of enamel maturation consists of an increase in mineralization within the developing tooth and concurrent loss of early-secreted matrix proteins. Exposure to fluoride during maturation causes a dose-related disruption of enamel mineralization resulting in widening gaps in its crystalline structure, excessive retention of enamel proteins, and increased porosity. These effects are thought to be due to fluoride's effect on the breakdown rates of matrix proteins and on the rate at which the by-products from that degradation are withdrawn from the maturing enamel (Aoba and Fejerskov 2002).

Clinically, mild forms of enamel fluorosis are evidenced by white horizontal striations on the tooth surface or opaque patches, usually located on the incisal edges of anterior teeth or cusp tips of posterior teeth. Opaque areas are visible in tangential reflected light but not in normal light. These lesions appear histopathologically as hypomineralization of the subsurface covered by a well-mineralized outer enamel surface (Thylstrup and Fejerskov 1978). In mild fluorosis, the enamel is usually smooth to the point of an explorer, but not in moderate and severe cases of the condition (Newbrun 1986). In moderate to severe forms of fluorosis, porosity increases and lesions extend toward the inner enamel. After the tooth erupts, its porous areas may flake off, leaving enamel defects where debris and bacteria can be trapped. The opaque areas can become stained yellow to brown, with more severe structural damage possible, primarily in the form of pitting of the tooth surface.

Enamel in the transitional or early maturation stage of development is the most susceptible to fluorosis (DenBesten and Thariani 1992). For most children, the first 6 to 8 years of life appear to be the critical period of risk. In the Ikeno district of Japan, where a water supply containing fluoride at 7.8 mg/L was inadvertently used for 12 years, no enamel fluorosis was seen in any child who was age 7 years or older at the start of this period or younger than 11 months old at the end of it (Ishii and Suckling 1991). For anterior teeth, which are of the most aesthetic concern, the risk period appears to be the first 3 years of life (Evans and Stamm 1991; Ishii and Suckling 1991; Levy et al. 2002a). Although it is possible for enamel fluorosis to occur when teeth are exposed during enamel maturation alone, it is unclear whether it will occur if fluoride exposure takes place only at the stage of enamel-matrix secretion. Fejerskov et al. (1994) noted that fluoride uptake into mature enamel is possible only as a result of concomitant enamel dissolution, such as caries development. Because the severity of fluorosis is related to the duration, timing, and dose of fluoride intake, cumulative exposure during the entire maturation stage, not merely during critical periods of certain types
of tooth development, is probably the most important exposure measure to consider when assessing the risk of fluorosis (DenBesten 1999).

Mechanisms

Dental enamel is formed by matrix-mediated biomineralization. Crystallites of hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) form a complex protein matrix that serves as a nucleation site (Newbrun 1986). The matrix consists primarily of amelogenin, proteins synthesized by secretory ameloblasts that have a functional role in establishing and maintaining the spacing between enamel crystallites. Full mineralization of enamel occurs when amelogenin fragments are removed from the extracellular space. The improper mineralization that occurs with enamel fluorosis is thought to be due to inhibition of the matrix proteinases responsible for removing amelogenin fragments. The delay in removal impairs crystal growth and makes the enamel more porous (Bronckers et al. 2002). DenBesten et al. (2002) showed that rats exposed to fluoride in drinking water at 50 or 100 mg/L had lower total proteinase activity per unit of protein than control rats. Fluoride apparently interferes with protease activities by decreasing free Ca$^{2+}$ concentrations in the mineralizing milieu (Aoba and Fejerskov 2002).

Matsuo et al. (1998) investigated the mechanism of enamel fluorosis in rats administered sodium fluoride (NaF) at 20 mg/kg by subcutaneous injections for 4 days or at 240 mg/L in drinking water for 4 weeks. They found that fluoride alters intracellular transport in the secretory ameloblasts and suggested that G proteins play a role in the transport disturbance. They found different immunoblotting-and-pertussis-toxin-sensitive G proteins on the rough endoplasmic reticulum and Golgi membranes of the germ cells of rats’ incisor teeth.

Health Issues and Clinical Treatment

Whether to consider enamel fluorosis, particularly the moderate to severe forms, an adverse cosmetic effect or an adverse health effect has been the subject of debate for decades. Some early literature suggests that the clinical course of caries could be compromised by untreated severe enamel fluorosis. Smith and Smith (1940, pp.1050-1051) observed, “There is ample evidence that mottled teeth, though they be somewhat more resistant to the onset of decay, are structurally weak, and that unfortunately when decay does set in, the result is often disastrous. Caries once started evidently spreads rapidly. Steps taken to repair the cavities in many cases were unsuccessful, the tooth breaking away when attempts were made to anchor the fillings, so that extraction was the only course.” Gruebbel (1952, p.153) expressed a similar viewpoint: “Severe mottling is as destructive to teeth as
is dental caries. Therefore, when the concentration is excessive, defluorination or a new water supply should be recommended. The need for removing excessive amounts of fluorides calls attention to the peculiar situation in public health practice in which a chemical substance is added to water in some localities to prevent a disease and the same chemical substance is removed in other localities to prevent another disease.” Dean advised that when the average child in a community has mild fluorosis (0.6 on his scale, described in the next section), “. . . it begins to constitute a public health problem warranting increasing consideration” (Dean 1942, p. 29).

There appears to be general acceptance in today’s dental literature that enamel fluorosis is a toxic effect of fluoride intake that, in its severest forms, can produce adverse effects on dental health, such as tooth function and caries experience. For example:

- “The most severe forms of fluorosis manifest as heavily stained, pitted, and friable enamel that can result in loss of dental function” (Burt and Eklund 1999).
- “In more severely fluorosed teeth, the enamel is pitted and discolored and is prone to fracture and wear” (ATSDR 2003, p. 19).
- “The degree of porosity (hypermineralization) of such teeth results in a diminished physical strength of the enamel, and parts of the superficial enamel may break away . . . In the most severe forms of dental fluorosis, the extent and degree of porosity within the enamel are so severe that most of the outermost enamel will be chipped off immediately following eruption” (Fejerskov et al. 1990, p. 694).
- “With increasing severity, the subsurface enamel all along the tooth becomes increasingly porous . . . the more severe forms are subject to extensive mechanical breakdown of the surface” (Aoba and Fejerskov 2002, p. 159).
- “With more severe forms of fluorosis, caries risk increases because of pitting and loss of the outer enamel” (Levy 2003, p. 286).
- “. . . the most severe forms of dental fluorosis might be more than a cosmetic defect if enough fluorotic enamel is fractured and lost to cause pain, adversely affect food choices, compromise chewing efficiency, and require complex dental treatment” (NRC 1993, p. 48).

Severe enamel fluorosis is treated to prevent further enamel loss and to address the cosmetic appearance of teeth. Treatments include bleaching, microabrasion, and the application of veneers or crowns. Bleaching and microabrasion are typically used with the mild to moderate forms of enamel fluorosis. Bleaching is the least invasive procedure, but does not eliminate the dark stains associated with severe enamel fluorosis. Microabrasion involves the controlled abrasion of enamel to remove superficial stains.
This technique has been reported to be minimally invasive and successful in treating single-line or patched opacities, but was not effective in treating defects that extend deeper into the enamel (Wong and Winter 2002). Train et al. (1996) found that while microabrasion improved the appearance of all degrees of enamel fluorosis, severely fluoroed teeth exhibited more defective surfaces following treatment. Pits and fissures can be filled with flowable composites. Partial veneers, composite veneers, and crowns provide the best aesthetic results for very severe enamel fluorosis, but are the most invasive treatments. Crowns are usually used as a last resort because they can be a threat to tooth vitality (Christensen 2005). The procedure requires the further removal of tooth enamel to allow for bonding of the crown, and sometimes requires replacement within a few years. The more invasive treatments should be used only in the most severe cases of enamel fluorosis.

Ascertaining Enamel Fluorosis

Enamel Fluorosis Indexes

The three main indexes used to grade enamel fluorosis in research are Dean’s index, the Thylstrup-Fejerskov index (TFI), and the tooth surface index of fluorosis (TSIF). A particularly useful review of the characteristics, strengths, and limitations of these indexes is given by Rozier (1994).

Dean’s index (Table 4-1) uses a 6-point ordinal scale, ranging from normal to severe, to classify individuals with regard to enamel fluorosis (Dean 1942). Scores are assigned on the basis of the two worst-affected teeth and are derived from an assessment of the whole tooth rather than the worst-affected tooth surface. Although Dean’s index is considered adequate for a broad definition of prevalence and trends, it suffers from limited sensitivity for analytical research in several ways. Because a person is assigned to a fluorosis category on the basis of only two severely affected teeth, the score may not discriminate between those individuals who have more affected teeth from those with only a few affected teeth. In addition, as the teeth most frequently affected by enamel fluorosis are posterior teeth and not the aesthetically important anterior teeth, Dean’s index may misclassify individuals with respect to aesthetic effects (Griffin et al. 2002). As a score assigned at the level of the person, Dean’s index enables the computation of prevalence estimates but does not permit an analysis of the effects of changes in exposure during the development of different teeth. Finally, with only one category for severe fluorosis, Dean’s index does not discriminate between staining and pitting or between discrete and confluent pitting. In fact, Dean revised the index in 1942 to create the version in use today, which combines the original “moderately severe” and “severe” categories. Despite its limitations, Dean’s index is by far the most widely used measure of enamel
### TABLE 4-1 Clinical Criteria for Dean’s Enamel Fluorosis Index

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (0)</td>
<td>The enamel represents the usually translucent semivitriform type of structure. The surface is smooth, glossy, and usually a pale creamy white color.</td>
</tr>
<tr>
<td>Questionable (0.5)</td>
<td>The enamel discloses slight aberrations from the translucency of normal enamel, ranging from a few white flecks to occasional white spots. This classification is utilized when a definite diagnosis of the mildest form of fluorosis is not warranted and a classification of “normal” is not justified.</td>
</tr>
<tr>
<td>Very mild (1)</td>
<td>Small, opaque, paper white area scattered irregularly over the tooth but not involving as much as approximately 25% of the tooth surface. Frequently included in this classification are teeth showing no more than 1 to 2 mm of white opacity at the tip of the summit of the cusps of the bicuspids or second molars.</td>
</tr>
<tr>
<td>Mild (2)</td>
<td>The white opaque areas in the enamel of the teeth are more extensive but do not involve as much as 50% of the tooth.</td>
</tr>
<tr>
<td>Moderate (3)</td>
<td>All enamel surfaces of the teeth are affected, and surfaces subject to attrition show marked wear. Brown stain is frequently a disfiguring feature.</td>
</tr>
<tr>
<td>Severe (4)</td>
<td>All enamel surfaces are affected and hypoplasia is so marked that the general form of the tooth may be altered. The major diagnostic sign of this classification is the discrete or confluent pitting. Brown stains are widespread and teeth often present a corroded appearance.</td>
</tr>
</tbody>
</table>

SOURCE: Dean 1942. Reprinted with permission; copyright 1942, American Association for the Advancement of Science.

Fluorosis in the research literature. As a consequence, any comprehensive review of the literature must rely upon it.

The TFI (Table 4-2), which classifies the facial surface of each tooth on a 10-point scale (0 to 9), provides more criteria and categories for characterizing mild and severe forms of fluorosis than Dean’s index allows (Thylstrup and Fejerskov 1978). At the upper end of the severity scale, the TFI usefully distinguishes among marked discoloration without pitting (score 4); discrete or focal pitting (score 5); and degrees of confluent pitting, enamel loss, and tooth deformation (scores 6-9). The TFI has been shown to be a valid indication of the fluoride content of fluorotic enamel. Most investigators combine TFI scores of 5 and higher, all of which include pitting, to form a category of severe enamel fluorosis.

The TSIF (Table 4-3) ascribes a fluorosis score on an 8-point scale (0 to 7) to each unrestored surface of each tooth (Horowitz et al. 1984). At the higher end of the scale, there is a greater range of criteria for characterization of effects. A TSIF score of 5 is the lowest classification on this scale that involves enamel pitting. Although some researchers combine scores 5-7
TABLE 4-2 Clinical Criteria and Scoring for the Thylstrup and Fejerskov Index (TFI) of Enamel Fluorosis

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal translucency of enamel remains after prolonged air-drying.</td>
</tr>
<tr>
<td>1</td>
<td>Narrow white lines corresponding to the perikymata.</td>
</tr>
<tr>
<td>2</td>
<td>Smooth surfaces: More pronounced lines of opacity that follow the perikymata. Occasionally confluence of adjacent lines. Occlusal surfaces: Scattered areas of opacity &lt; 2 mm in diameter and pronounced opacity of cuspal ridges.</td>
</tr>
<tr>
<td>3</td>
<td>Smooth surfaces: Merging and irregular cloudy areas of opacity. Accentuated drawing of perikymata often visible between opacities. Occlusal surfaces: Confluent areas of marked opacity. Worn areas appear almost normal but usually circumscribed by a rim of opaque enamel.</td>
</tr>
<tr>
<td>4</td>
<td>Smooth surfaces: The entire surface exhibits marked opacity or appears chalky white. Parts of surface exposed to attrition appear less affected. Occlusal surfaces: Entire surface exhibits marked opacity. Attrition is often pronounced shortly after eruption.</td>
</tr>
<tr>
<td>5</td>
<td>Smooth and occlusal surfaces: Entire surface displays marked opacity with focal loss of outermost enamel (pits) &lt; 2 mm in diameter.</td>
</tr>
<tr>
<td>6</td>
<td>Smooth surfaces: Pits are regularly arranged in horizontal bands &lt; 2 mm in vertical extension. Occlusal surfaces: Confluent areas &lt; 3 mm in diameter exhibit loss of enamel. Marked attrition.</td>
</tr>
<tr>
<td>7</td>
<td>Smooth surfaces: Loss of outermost enamel in irregular areas involving less than half of entire surface. Occlusal surfaces: Changes in morphology caused by merging pits and marked attrition.</td>
</tr>
<tr>
<td>8</td>
<td>Smooth and occlusal surfaces: Loss of outermost enamel involving more than half of surface.</td>
</tr>
<tr>
<td>9</td>
<td>Smooth and occlusal surfaces: Loss of main part of enamel with change in anatomic appearance of surface. Cervical rim of almost unaffected enamel is often noted.</td>
</tr>
</tbody>
</table>


to classify severe enamel fluorosis, others extend their highest category of severity to include score 4, which includes staining but not pitting.

Other fluorosis indexes, such as those developed by Siddiqui (1955) and Al-Alousi et al. (1975), are used less frequently in research and almost never in the United States. The developmental defects of enamel (DDE) index was designed as a general classification scheme for enamel defects (FDI 1982; Clarkson and O’Mullane 1989). As it emphasizes aesthetic concerns and is not based on etiologic considerations, it is not technically an index of enamel fluorosis. The fluorosis risk index (FRI) was developed specifically for use in case-control studies (Pendrys 1990), very few of which have been conducted.
TABLE 4-3 Clinical Criteria and Scoring for the Tooth Surface Index of Fluorosis (TSIF)

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Enamel shows no evidence of fluorosis.</td>
</tr>
<tr>
<td>1</td>
<td>Enamel shows definite evidence of fluorosis—namely, areas with parchment-white color that total less than one-third of the visible enamel surface. This category includes fluorosis confined only to incisal edges of anterior teeth and cusp tips of posterior teeth (“snowcapping”).</td>
</tr>
<tr>
<td>2</td>
<td>Parchment-white fluorosis totals at least one-third, but less than two-thirds, of the visible surface.</td>
</tr>
<tr>
<td>3</td>
<td>Parchment-white fluorosis totals at least two-thirds of the visible surface.</td>
</tr>
<tr>
<td>4</td>
<td>Enamel shows staining in conjunction with any of the preceding levels of fluorosis. Staining is defined as an area of definite discoloration that may range from light to very dark brown.</td>
</tr>
<tr>
<td>5</td>
<td>Discrete pitting of the enamel exists, unaccompanied by evidence of staining of intact enamel. A pit is defined as a definite physical defect in the enamel surface with a rough floor that is surrounded by a wall of intact enamel. The pitted area is usually stained or differs in color from the surrounding enamel.</td>
</tr>
<tr>
<td>6</td>
<td>Both discrete pitting and staining of the intact enamel exist.</td>
</tr>
<tr>
<td>7</td>
<td>Confluent pitting of the enamel surface exists. Large areas of enamel may be missing and the anatomy of the tooth may be altered. Dark-brown stain is usually present.</td>
</tr>
</tbody>
</table>


A major difference among the three principal enamel fluorosis indexes is the level at which the scores are recorded: the level of the person on Dean’s index, the level of the tooth on the TFI, and the level of the tooth surface on the TSIF. As the tooth-level scores for Dean’s index are usually recorded but not reported, it is impossible to break the reported person-level scores down to the tooth or tooth-surface level. Similarly, the tooth level TFI scores cannot be broken down to the level of the tooth surface. In contrast, it is possible to combine TFI scores up to the person level and to combine TSIF scores up to the tooth or person levels.

Because the person-level Dean’s index is the oldest and still the most widely used enamel fluorosis index, researchers using the TFI or TSIF sometimes, though rarely, aggregate scores on those scales up to the person level for comparability. When this is done, the most severe one or two teeth or tooth surfaces are typically used. As a consequence, the prevalence of a given level of enamel fluorosis severity (other than “normal” or “unaffected”) will tend to be lowest if expressed as a proportion of all tooth surfaces, intermediate in magnitude if expressed as a proportion of all teeth, and highest if expressed as a proportion of all persons in a given sample. Prevalence estimates at the person level are reviewed by the committee later in this chapter. When the interest is in aesthetic concerns about milder forms of fluorosis,
the person level and tooth level have disadvantages, as the affected teeth may be located in the posterior part of the mouth and thus less visible under ordinary (nonclinical) circumstances. For the severest forms, in contrast, the considerations are reversed. It is more informative to know the proportion of a population who have any teeth with dark staining and pitting than the proportion of all teeth or of all tooth surfaces that have these most severe manifestations of enamel fluorosis.

**Diagnostic Issues**

The 1993 National Research Council (NRC) report found that the accuracy of clinical diagnosis of fluorotic lesions, especially those of the mild form, has been plagued by the fact that not all white or light yellow opacities in dental enamel are caused by fluoride. The ascertainment of severe enamel fluorosis, in contrast, is much more secure. This is especially true in studies of children in communities with relatively high water fluoride concentrations in the United States and similar locales, where there are few if any alternative explanations for dark yellow to brown staining and pitting of the enamel of recently erupted permanent teeth.

Some studies in the international literature have reported severe mottling of the teeth that could not be attributed to fluoride exposure. For example, Whitford (1996) was unable to explain a high prevalence of severe lesions resembling fluorosis in individuals in Morrococha, Peru, on the basis of exposure to fluoride in water, food, or dental products. Yoder et al. (1998) found severe dental mottling in a population in Tanzania with negligible fluoride in the water (<0.2 mg/L). They noted that urinary fluoride concentrations in affected subjects from that area were not consistent with concentrations found in subjects from a high-fluoride area who had severe enamel fluorosis. Mottling unrelated to fluoride has been suggested to be due to malnutrition, metabolic disorders, exposure to certain dietary trace elements, widespread introduction of tea drinking among children at very early ages, or physical trauma to the tooth (Curzon and Spector 1977; Cutress and Suckling 1990).

A genetic condition called amelogeneis imperfecta causes enamel defects that can be mistaken for enamel fluorosis (Seow 1993); the hypoplastic lesions of this condition have a deficiency in the quantity of enamel with grooves and pits on the surface. Hypocalcified lesions have low mineralization, appear pigmented, and have softened and easily detachable enamel. Hypomaturation conditions are evident as opaque and porous enamel. The prevalence of amelogeneis imperfecta ranges from approximately 1 in 700 to 1 in 14,000, depending on the population studied (Seow 1993).

Angmar-Mansson and Whitford (1990) reported that acute and chronic exposures to hypobaric hypoxia that occurs at high altitudes are associated
with bilaterally symmetrical and diffuse disturbances in enamel mineralization that might be mistaken for fluorosis. More recently, Rweneyonyi et al. (1999) reported higher prevalences of severe enamel fluorosis at higher altitudes than at lower altitudes in Ugandan populations with the same water fluoride levels.

Some evidence from animal studies indicates that genetics might contribute to susceptibility to enamel fluorosis (Everett et al. 2002). It has also been proposed that use of the antibiotic amoxicillin during infancy might contribute to the development of enamel fluorosis of the primary teeth (Hong et al. 2004).

A number of review articles evaluate the strengths and deficiencies of the various indexes used to diagnose and characterize the degree of enamel fluorosis (Clarkson 1989; Ellwood et al. 1994; Kingman 1994; Rozier 1994). In general, the following observations may be made:

- The various indexes use different examination techniques, classification criteria, and ways of reporting data. All indexes are based on subjective assessment, and little information is available on their validity or comparability. Prevalence data obtained from these indexes also can vary considerably because of differences in study protocols and case definitions. Nevertheless, the American Dental Association (2005) considers severe and even moderate fluorosis “typically easy to detect.”

- Examiner reliability is an important consideration in evaluation studies. Systematic interexaminer variability has been reported (Burt et al. 2003). Rozier (1994) noted that only about half the studies available in 1994 provided evidence that examiner reliability was evaluated. Although almost all of those assessments were conducted in populations in which severe enamel fluorosis was very rare, they showed an acceptable level of agreement.

- Agreement among examiners tends to be lower when enamel fluorosis is recorded at the level of the tooth or tooth surface than when it is recorded at the person level.

Prevalence of Severe Enamel Fluorosis in Relation to Water Fluoride Concentrations

In many reviews and individual studies, all levels of enamel fluorosis severity are grouped together. This approach is less problematic at comparatively low levels of fluoride intake, where all or almost all of the cases are mild or moderate in severity. At higher intake levels, such as those typically found in communities with water fluoride concentrations at the current MCLG of 4 mg/L or the current SMCL of 2 mg/L, it is more informative to report results for the different levels of fluorosis severity. Those reviews in
which severity distinctions have been drawn, such as NRC (1993) and IOM (1997), have tended to combine moderate and severe fluorosis into a single category. The present report focuses more specifically on the severe forms.

The committee compiled prevalence estimates at the person level for severe enamel fluorosis in relation to water fluoride levels from studies around the world. The starting points were the estimates provided in EPA’s documentation supporting the MCLG (50 Fed. Reg. 20164 [1985]) and Appendix C6 of McDonagh et al. (2000a). To these were added results from 24 additional studies (Venkateswarlu et al. 1952; Forsman 1974; Retief et al. 1979; Rozier and Dudney 1981; Subbareddy and Tewari 1985; Haimanot et al. 1987; Kaur et al. 1987; Mann et al. 1987, 1990; Szpunar and Burt 1988; Thaper et al. 1989; Jackson et al. 1995; Cortes et al. 1996; Akpata et al. 1997; Gopalakrishnan et al. 1999; Kumar and Swango 1999; Menon and Indushekar 1999; Rwenyonyi et al. 1999; Sampaio and Arneberg 1999; Awadia et al. 2000; Alarcón-Herrera et al. 2001; Grobler et al. 2001; Ermiş et al. 2003; Wondwossen et al. 2004). Results were excluded if they were for fluorosis indexes other Dean’s index, the TFI, the TSIF, or modifications thereof (e.g., Goward 1982; Nunn et al. 1992); for all fluorosis or for moderate and severe fluorosis combined (e.g., Warnakulasuriya et al. 1992; Mella et al. 1994; Alonge et al. 2000; Burt et al. 2003); for primary or deciduous teeth as opposed to permanent teeth (e.g., McInnes et al. 1982); for different teeth separately with no results at the person level or for all teeth combined (e.g., Opinya et al. 1991); for unbounded upper categories of water fluoride for which no mean or median value was given (e.g., > 1.2 mg/L in Heller et al. [1997], > 2 mg/L in Ray et al. [1982], > 2.5 mg/L in Angelillo et al. [1999]); for bounded but extremely wide water fluoride ranges (e.g., 0.8 to 4.3 mg/L in Haimanot et al. [1987], 0.7 to 4.0 in Beltran-Aguilar et al. [2002], 0.3 to 2.2 mg/L in Wondwossen et al. [2004]). For narrower bounded categories, the midrange water fluoride level was used. Results from studies of children and teenagers (age 20 years or younger) were tallied separately from results for adults. Severe enamel fluorosis was classified as the “severe” classification in Dean’s index and, depending on the groupings created by the original investigators, TFI scores of 4-9 or 5-9 and TSIF scores of 4-7 or 5-7. Because of the wide variability in methods and populations, and the lack of independence when a given study provided more than one result, the estimates were not subjected to formal statistical analyses. Instead, plots of the prevalence estimates in relation to water fluoride concentration were examined for the presence of any clear and obvious patterns or trends.

Figure 4-1 shows 94 prevalence estimates from studies in the United States. Despite the wide range of research methods, fluorosis indexes, water fluoride measurement methods, and population characteristics in these studies conducted over a period spanning half a century, a clear trend is evident.
The prevalence of severe enamel fluorosis is close to zero in communities at all water fluoride concentrations below 2 mg/L. Above 2 mg/L, the prevalence rises sharply. The shape of this curve differs dramatically from the linear trend observed when all levels of fluorosis severity are combined and related to either the water fluoride concentration (Dean 1942) or the estimated daily dose in milligrams per kilogram (Fejerskov et al. 1990).

Not shown in Figure 4-1 are a prevalence of 54% in a community with a water fluoride concentration of 14 mg/L (50 Fed. Reg. 20164 [1985]) and results from two studies of adults. One, with an age range of 20-44 years, reported prevalences of zero at <0.1 mg/L and 2% at 2.5 mg/L (Russell and Elvove 1951). In the other, with an age range of 27-65 years, the prevalences were zero at 0.7 mg/L and 76% at 3.5 mg/L (Eklund et al. 1987). These results are broadly consistent with those in Figure 4-1.

Strongly supporting evidence comes from a series of surveys conducted by researchers at the National Institute of Dental Health (Selwitz et al. 1995, 1998). In these studies using the TSIF, scores were reported only at the tooth-surface level (Figure 4-2). As with the person-level prevalence estimates (Figure 4-1), an approximate population threshold for severe enamel fluorosis is evident at water concentrations below 2 mg/L.
Figure 4-3 shows 143 prevalence estimates from studies of children outside the United States. Not shown are results for three Ethiopian communities with extremely high water fluoride concentrations of 26, 34 and 36 mg/L and prevalences of 18%, 48% and 25%, respectively (Haimanot et al. 1987). Although a positive association may be discernible, it is much less obvious than in the U.S. studies. There is little evidence of an approximate population threshold as in the results in U.S. communities (Figure 4-1). In many regions around the world, water intake among children whose permanent teeth are forming can be much more variable than in the United States, susceptibility may differ more widely, sources of fluoride intake other than the community water supply may be more prevalent, or the ascertainment of severe enamel fluorosis may be more often compromised by other determinants of dental discoloration and pitting.

One question is whether the most severe forms of enamel fluorosis, specifically those involving confluent pitting, occur at water concentrations in the range of the current MCLG of 4 mg/L. This question cannot be an-
FIGURE 4-3 Prevalence of severe enamel fluorosis at the person level by water fluoride concentration, permanent teeth, age < 20 years, communities outside the United States.

Answered by most studies, which use Dean’s 1942 modification of his index combining “moderately severe” and “severe” classifications of his original system (Dean 1934) into a single category (Dean 1942; Rozier 1994). Three studies, however, in U.S. communities with water fluoride concentrations of approximately 4 mg/L have used enamel fluorosis indexes that draw severity distinctions within the “severe” category.

In Lowell, Indiana, with a water fluoride concentration of approximately 4 mg/L, 7% of a 1992 sample and 2% of a 1994 sample of children 7-14 years of age had at least one tooth surface assigned the highest possible TSIF score of 7 (Table 4-4). Expressed as a percentage of all tooth surfaces examined (mean, 32.3 per child), the prevalence of TSIF score 7 in the 1992 sample was substantially lower at 0.5% (Jackson et al. 1995). The lower prevalence using this metric is not surprising, as it includes surfaces on anterior teeth, which are not generally as susceptible to fluorosis as molars and other teeth located farther back in the mouth.

In Bushnell, Illinois, with a mean water fluoride concentration of 3.8 mg/L, samples of children age 8-10 years and 13-15 years were examined in 1980 and 1985 (Heifetz et al. 1988). As shown in Table 4-5, the TSIF score
**TABLE 4-4** Maximum TSIF Scores in Two Samples of Children Age 7-14 Years in a U.S. Community with a Water Fluoride Concentration of 4.0 mg/L

<table>
<thead>
<tr>
<th>Maximum TSIF Score</th>
<th>1992 study</th>
<th>1994 study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Children</td>
<td>Percent</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>7.9</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>22.8</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>16.8</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>25.7</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>9.9</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>6.9</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>100.0</td>
</tr>
</tbody>
</table>

SOURCE: Jackson et al. 1995, 1999; R.D. Jackson (Indiana University-Purdue University Indianapolis, personal commun., December 21, 2005).

**TABLE 4-5** Percentage of Tooth Surfaces Assigned TSIF Scores in Four Samples of Children Age 8-10 Years and 13-15 Years in a U.S. Community with a Water Fluoride Concentration of 3.8 mg/L

<table>
<thead>
<tr>
<th>TSIF Score</th>
<th>Age 8-10 (n = 59)</th>
<th>Age 13-15 (n = 34)</th>
<th>Age 8-10 (n = 62)</th>
<th>Age 13-15 (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30.3</td>
<td>36.9</td>
<td>24.2</td>
<td>22.5</td>
</tr>
<tr>
<td>1</td>
<td>28.5</td>
<td>25.6</td>
<td>32.2</td>
<td>30.8</td>
</tr>
<tr>
<td>2</td>
<td>17.1</td>
<td>16.7</td>
<td>18.7</td>
<td>18.8</td>
</tr>
<tr>
<td>3</td>
<td>19.7</td>
<td>18.6</td>
<td>19.7</td>
<td>22.1</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>1.3</td>
<td>3.1</td>
<td>3.9</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>0.5</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*The numbers of children (n) are given in parentheses. The numbers of tooth surfaces examined were not reported.


of 7 was assigned in all four samples. Detailed TSIF scores from this study are available only on as a percentage of all tooth surfaces examined. These results are consistent with those from the 1992 sample in Lowell, Indiana (Jackson et al. 1995) using the same fluorosis metric.
Confluent enamel pitting must be present for a tooth surface to be assigned a score of 7 on the TSIF scale (Table 4-3). In addition to the usual presence of dark brown staining, large areas of enamel may be missing and gross tooth structure may be altered as well. Thus, it has been sufficiently well documented that the most severe forms of enamel fluorosis for which classifications exist occur in children who reside in communities with water fluoride concentrations at or near the MCLG of 4 mg/L.

A third study, confined to the age range of 27-65 years, included a sample of 192 adults from Lordsburg, New Mexico, with a water fluoride concentration of 3.5 mg/L (Eklund et al. 1987). All members of this sample were native to Lordsburg and long-term residents of that community. The prevalence of severe fluorosis on Dean’s 1942 scale was extremely high in this sample, 76% overall. The investigators modified Dean’s scale specifically to split the “severe” category into ‘severe’ (discrete pitting) and ‘very severe’ (confluent pitting)” (Eklund et al. 1987). About half of those with more than moderate fluorosis were classified in the “very severe” category. These results for New Mexico adults are consistent with the results for children in Indiana and Illinois.

A reduction of all water fluoride concentrations to below 2 mg/L would be expected to make severe enamel fluorosis an extreme rarity in the United States, but would not be expected to eliminate it entirely. Isolated cases could still occur from excessive fluoride exposure from other sources, such as toothpaste swallowing and use of fluoride supplements and rinses. One can never rule out the possible existence of hypersusceptible individuals. Finally, though the ascertainment of severe enamel fluorosis is usually quite accurate in the United States, especially among children, it might be possible for dark yellow or brown staining and enamel pitting from other causes to be misdiagnosed as fluorosis. Such false positives might be particularly common among adults who are long-term users of smoked and smokeless tobacco products, heavy consumers of beverages such as coffee and tea, and perhaps some with special occupational exposures.

Aesthetic and Psychological Consequences of Enamel Fluorosis

Studies show that facial attractiveness is important and that attractive people are judged to be more socially desirable than less attractive people (Berscheid and Walster 1974; Adams and Huston 1975; Adams 1977; Jenny and Proshek 1986). Newton et al. (2003) assessed the impact of modified images of untreated cavities on front teeth on the appraisal of personal characteristics in the United Kingdom. Study participants associated decayed and discolored teeth with lower intelligence and social competence and with poor psychological adjustment. Interestingly, the ratings depended on the facial appearance studied, an indication that the impact of enamel
fluorosis is less noticeable in a more attractive face. Although studies of the attractiveness of teeth are sparse, the orthodontic literature has shown that more than 80% of patients seek care out of concern for aesthetics, rather than health or function (Albino et al. 1981).

The potential for psychological and behavioral problems to develop from the aesthetically displeasing consequences of enamel fluorosis has been a long-standing concern. In 1984, an ad hoc panel of behavioral scientists convened by the U.S. Environmental Protection Agency (EPA) and the National Institute of Mental Health to evaluate the issue concluded that “individuals who have suffered impaired dental appearance as a result of moderate and severe fluorosis are probably at increased risk for psychological and behavioral problems or difficulties” (R.E. Kleck, unpublished report, Nov. 17, 1984, as cited in 50 Fed. Reg. 20164 [1985]). The panel recommended research on the social, emotional, and behavioral effects of enamel fluorosis.

Few studies have assessed the association between the public’s perceived aesthetic problems and degree of enamel fluorosis. Only one of those studies was conducted in the United States. Lalumandier and Rozier (1998) found that parental satisfaction with the color of their children’s teeth decreased as the severity of fluorosis increased. Although 73.9% of parents were satisfied with the color of teeth in the absence of enamel fluorosis, only 24.2% of parents were satisfied with the color of their children’s teeth when the TSIF score was 4 or greater (moderate to severe forms). In a study of dental students’ perceptions, Levy et al. (2002b) observed that fluorosis and nonfluorosis images were consistently rated more favorably by fourth-year students than by the same students in their first year. According to the authors, the results suggested that dentists might regard fluorosis with less concern given that they are exposed to a wide range of oral conditions, whereas those outside the dental profession might view fluorosis with more concern. Griffin et al. (2002) reviewed five published studies of aesthetic perception and enamel fluorosis and estimated that approximately 2% of U.S. schoolchildren might experience perceived aesthetic problems from exposure to fluoride at 0.7-1.2 mg/L. It should be noted that perceived aesthetic problems have also been reported even in the absence of enamel fluorosis because of nonfluorotic enamel opacities and hypoplasia, natural yellowish appearance of teeth, and discoloration due to dental caries. For example, Griffin et al. (2002) also noted that the percentage of respondents with no fluorosis who were not satisfied with the appearance of their teeth ranged from 18% to 41%.

In general, studies conducted in other parts of the world show that the level of satisfaction expressed by parents, children, and dentists with the appearance of enamel fluorosis decreases with increasing severity of enamel fluorosis (Clark et al. 1993; Riordan 1993; Clark 1995; Hawley et al. 1996;
Lalumandier and Rozier 1998; Griffin et al. 2002). In contrast with those studies, Ismail et al. (1993) did not find enamel fluorosis to be an aesthetic problem in Truro, Nova Scotia. The primary reason for disliking the color of front teeth was perceived yellowness unrelated to enamel fluorosis. Similarly, a study conducted in Brazil found that enamel fluorosis had no impact on children’s self-perception of appearance (Peres et al. 2003).

A systematic review of water fluoridation estimated the proportion of the population likely to have aesthetic concerns about enamel fluorosis on the basis of a review of 88 studies (McDonagh et al. 2000a). The authors pointed out that the differences in the proportion of the population having enamel fluorosis of aesthetic concern with low concentrations of fluoride in drinking water and with fluoride at 1.2 mg/L were not statistically significant. However, the estimation of aesthetic concerns was based solely on a study conducted in Great Britain (Hawley et al. 1996) in which 14-year-old children from Manchester were asked to rate the appearance of life-sized pictures of two front teeth with enamel fluorosis (lips cropped off) classified by the TFI. According to the authors, the percentage of subjects who considered the appearance of the teeth unacceptable decreased from 29% for TF scores of 0 to 15% for TF scores of 2 and increased to 85% for TF scores of 4. Using those data, McDonagh et al. (2000a) defined enamel fluorosis of aesthetic concern as a case with a TF score of 3 or more, Dean’s score of “mild” or worse, and a TSIF score of 2 or more. With this definition, McDonagh et al. (2000a) estimated the prevalence of fluorosis of aesthetic concern in the United Kingdom to be 63% at 4 mg/L and 25% at 2 mg/L. For lower water fluoride concentrations, the estimated prevalence ranged from 15% at 1.2 mg/L down to a baseline of 6% at 0.1 mg/L.

The committee judges that this analysis produced an overestimation of the prevalence of fluorosis of actual aesthetic concern for two main reasons. First, McDonagh et al. (2000a) applied the aesthetic concerns expressed by study participants about fluorosis on front teeth to fluorosis prevalence studies that included posterior teeth, which have much less potential to pose aesthetic problems. Second, the analysis did not take into account the observation by Hawley et al. (1996) that a higher percentage of children found teeth with milder forms of enamel fluorosis (TF scores lower than 3) aesthetically preferable to normal teeth; almost one-third of the children rated the photograph of teeth with no fluorosis as unacceptable.

There have been no new studies of the prevalence of moderate enamel fluorosis in U.S. populations since the early 1990s. Previous estimates ranged from 4% to 15% (50 Fed. Reg. 20164 [1985]). These estimates are based on studies that used classification indexes for scoring enamel fluorosis, and are not based on an assessment of aesthetics. None of the available indexes allow for making distinctions between fluorosis on the anterior and posterior teeth, so the percentage of children with moderate enamel fluorosis...
of aesthetic concern could not be determined, but the percentage would be lower than 15%.

The committee found only one study (Morgan et al. 1998) that specifically evaluated the psychological and behavioral impacts of enamel fluorosis on children with the condition. A group of 197 pediatric patients of a dental practice between the ages of 7 and 11 were examined for enamel fluorosis. Their parents completed the Child Behavior Checklist (CBCL), a widely used measure of behavioral problems in studies of children. The study found no substantial differences between groups classified by degree of fluorosis in overall CBCL scores or in scores on two subscales: externalizing (aggressive, hyperactive and antisocial behaviors typical of undercontrol or “acting out”) and internalizing (behaviors of social withdrawal, depression and anxiety typical of overcontrol or inhibition). The study was limited by the fact that an aggregate measure of fluoride exposure was unrelated to enamel fluorosis and few if any of the children had severe enamel fluorosis.

Several methodologic issues have hindered the assessment of the aesthetic importance of unattractive teeth in general and enamel fluorosis in particular. First, assessing the perception of aesthetics is by its very nature subjective. Second, it is not clear who should make judgments about the aesthetic appearance of teeth. The perceptions of the affected individual, as a child and in subsequent life, as well as those of parents, friends, teachers, and other acquaintances can all be important. A sizeable proportion of parents and children have expressed dissatisfaction with the color of teeth even in the absence of enamel fluorosis. On the other hand, judgments made by professionals might not reflect the perception of the public. Third, it is difficult to place the condition of enamel fluorosis into the context of an overall aesthetic assessment of a person’s appearance or facial attractiveness. Cultural influences can play a role in how the condition is perceived. It also appears that perceptions of the appearance of teeth can be modified by the attractiveness of other facial features. Fourth, when the public or dental professionals are asked to assess aesthetic acceptability, their perceptions might change during the evaluation session.

From the standpoint of this committee’s charge to consider effects of relatively high levels of water fluoride, the main points to note are that the emphasis of research and discussion on psychological, behavioral, and social effects of enamel fluorosis has been almost entirely on children and on the mild and moderate forms of the condition that are more typical of lower fluoride exposure levels. Research needs to focus specifically on severe enamel fluorosis in those areas in which it occurs with appreciable frequency. In addition, research needs to include not only affected children while they are still children, but after they move into adulthood. Finally, parents might experience psychological and behavioral effects when their children develop
enamel fluorosis, especially in its moderate and severe forms. Unfortunately, research on parental effects is completely lacking.

Dental Caries in Relation to Water Fluoride Concentrations of 2 mg/L and Higher

Many reports have discussed the inverse relationship between dental caries and water fluoride at concentrations considerably lower than the current MCLG of 4 mg/L and SMCL of 2 mg/L (Dean 1942; PHS 1991; McDonagh et al. 2000a; CDC 2001). Fewer studies have been conducted in the United States of overall caries experience in communities with naturally occurring fluoride concentrations higher than those produced by fluoridation. The studies of children are shown in Table 4-6. One study suggested that the overall frequency of caries is reduced at approximately 4 mg/L compared with approximately 1 mg/L (Englander and DePaola 1979). A study of New Mexico adults gave similar results (Eklund et al. 1987). Another study suggested little or no difference (Jackson et al. 1995) and another gave mixed results (Selwitz et al. 1995). The evidence from these studies is not persuasive that caries frequency is appreciably lower at approximately 4 mg/L than at approximately 2 mg/L or 3 mg/L. The evidence from studies conducted in other countries is no more consistent (Binder 1973; Olsson 1979; Kunzel 1980; Chen 1989; Lewis et al. 1992; Warnakulasuriya et al. 1992; Yoder et al. 1998; Angelillo et al. 1999; Grobler et al. 2001).

Dental Caries in Relation to Severe Enamel Fluorosis

As previously noted, it is suspected within the dental research community that the enamel pitting that occurs in severe fluorosis might increase caries risk by reducing the thickness of the protective enamel layer and by allowing food and plaque to become entrapped in enamel defects. The possibility is thus raised that in a community with a water fluoride concentration high enough to produce an appreciable prevalence of severe fluorosis, the specific subset of children who develop this condition might be placed at increased caries risk, independent of the effect of the fluoride itself on the remainder of the population. The population of interest consists of those children who develop severe enamel fluorosis at 4 mg/L. If the water fluoride concentration were reduced to below 2 mg/L, few if any of these children would still develop severe enamel fluorosis. Many of them would develop mild to moderate fluorosis, however, while others might develop no fluorosis. It would be unreasonable, however, to assume that some children would skip all the way down from severe fluorosis to no fluorosis when the water concentration is reduced, while others would have mild to moderate fluorosis at either concentration. As the desired fluorosis severity
### TABLE 4-6 Mean Number of Decayed, Missing and Filled Surfaces (DMFS) in Permanent Teeth by Water Fluoride Concentration in Studies of Children in U.S. Communities with Water Fluoride Concentrations at or Near the MCLG of 4 mg/L

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Year</th>
<th>Community</th>
<th>Number of Children</th>
<th>Approximate Water Fluoride Concentration (mg/L)</th>
<th>Mean DMFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Englander and DePaola (1979)</td>
<td>12-15</td>
<td>NA</td>
<td>Kalamazoo, MI</td>
<td>315</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stickney, IL</td>
<td>312</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Charlotte, NC</td>
<td>213</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Midland, TX</td>
<td>311</td>
<td>5-7</td>
<td>2.4</td>
</tr>
<tr>
<td>Driscoll et al. (1983)</td>
<td>8-11</td>
<td>1980</td>
<td>Kewanee, IL</td>
<td>157</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monmouth, IL</td>
<td>80</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abindgon and Elmwood, IL</td>
<td>110</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bushnell, Ipava and Table Grove, IL</td>
<td>77</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Driscoll et al. (1983)</td>
<td>12-16</td>
<td>1980</td>
<td>Kewanee, IL</td>
<td>179</td>
<td>1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monmouth, IL</td>
<td>63</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abindgon and Elmwood, IL</td>
<td>82</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bushnell, Ipava and Table Grove, IL</td>
<td>59</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Heifetz et al. (1988)</td>
<td>8-10</td>
<td>1985</td>
<td>Kewanee, IL</td>
<td>156</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monmouth, IL</td>
<td>102</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abindgon and Elmwood, IL</td>
<td>112</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bushnell, Ipava and Table Grove, IL</td>
<td>62</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Heifetz et al. (1988)</td>
<td>13-15</td>
<td>1985</td>
<td>Kewanee, IL</td>
<td>94</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monmouth, IL</td>
<td>23</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abindgon and Elmwood, IL</td>
<td>47</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bushnell, Ipava and Table Grove, IL</td>
<td>29</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>Selwitz et al. (1995)</td>
<td>8-10, 14-16</td>
<td>1990</td>
<td>Kewanee, IL</td>
<td>258</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monmouth, IL</td>
<td>105</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abindgon and Elmwood, IL</td>
<td>117</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bushnell, Ipava and Table Grove, IL</td>
<td>77</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Jackson et al. (1995)</td>
<td>7-14</td>
<td>1992</td>
<td>Brownsburg, IN</td>
<td>117</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lowell, IN</td>
<td>101</td>
<td>4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

NA: Not available.
distribution is inherently unknown, a conservative approach is to compare
the children with severe fluorosis at 4 mg/L with children from their own
communities with mild to moderate fluorosis.

Results for such comparisons are summarized in Table 4-7 for studies
reporting the mean number of decayed, missing and filled tooth surfaces
(DMFS), in Table 4-8 for studies reporting the number of decayed, missing
and filled teeth (DMFT), and in Table 4-9 for studies reporting the per-

TABLE 4-7 Mean Number of Decayed, Missing, and Filled Permanent
Tooth Surfaces (DMFS) among Children with Severe and Mild to
Moderate Enamel Fluorosis

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Age (years)</th>
<th>Number of Children</th>
<th>Fluorosis Index and Range</th>
<th>Mean DMFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>8-16</td>
<td>218</td>
<td>Dean very mild to moderate 1.6</td>
<td></td>
</tr>
<tr>
<td>(Driscoll et al. 1986)</td>
<td>8-16</td>
<td>54</td>
<td>Dean severe               3.0</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>15-16</td>
<td>83</td>
<td>Dean very mild to moderate 4.4</td>
<td></td>
</tr>
<tr>
<td>(Mann et al. 1987)</td>
<td>15-16</td>
<td>46</td>
<td>Dean severe               10.4</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>8-10</td>
<td>55</td>
<td>Dean very mild to moderate 1.2</td>
<td></td>
</tr>
<tr>
<td>(Mann et al. 1990)</td>
<td>8-10</td>
<td>6</td>
<td>Dean severe               1.8</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>12-14</td>
<td>24</td>
<td>TSIF 1-3                 1.7</td>
<td></td>
</tr>
<tr>
<td>(Ermiş et al. 2003)</td>
<td>12-14</td>
<td>105</td>
<td>TSIF 4-7                 1.9</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 4-8 Mean Numbers of Decayed, Missing, and Filled Permanent
Teeth (DMFT) among Children with Severe and Mild to Moderate
Enamel Fluorosis

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Age (years)</th>
<th>Number of Children</th>
<th>Fluorosis Index and Range</th>
<th>Mean DMFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>6-16</td>
<td>1,290</td>
<td>Dean very mild to moderate 1.7</td>
<td></td>
</tr>
<tr>
<td>(Chen 1989)</td>
<td>6-16</td>
<td>10</td>
<td>Dean severe               2.5</td>
<td></td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>14</td>
<td>44</td>
<td>Dean mild                 3.4</td>
<td></td>
</tr>
<tr>
<td>(Warnakulasuriya et al. 1992)</td>
<td>14</td>
<td>48</td>
<td>Dean moderate to severe   3.3</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>6-12</td>
<td>42</td>
<td>TFI 3-4                   1.1</td>
<td></td>
</tr>
<tr>
<td>(Cortes et al. 1996)</td>
<td>6-12</td>
<td>18</td>
<td>TFI ≥5                    1.3</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>12-14</td>
<td>24</td>
<td>TSIF 1-3                  1.2</td>
<td></td>
</tr>
<tr>
<td>(Ermiş et al. 2003)</td>
<td>12-14</td>
<td>105</td>
<td>TSIF 4-7                  1.3</td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>12-15</td>
<td>87</td>
<td>TFI 3-4                   1.5</td>
<td></td>
</tr>
<tr>
<td>(Wondwossen et al. 2004)</td>
<td>12-15</td>
<td>89</td>
<td>TFI 5-7                   2.4</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4-9 Percentage of Teeth Scored as Decayed, Missing, Filled, or with Caries among Children and Adults with Severe and Mild-to-Moderate Enamel Fluorosis

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Age (years)</th>
<th>Teeth</th>
<th>Number of Persons</th>
<th>Range of Dean’s Fluorosis Index</th>
<th>Measure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia (Olsson 1979)</td>
<td>6-7, 13-14</td>
<td>All</td>
<td>Mild to moderate</td>
<td>Cavities 25</td>
<td>9</td>
</tr>
<tr>
<td>United States (Driscoll et al. 1986)</td>
<td>8-16</td>
<td>All</td>
<td>218</td>
<td>Very mild to moderate</td>
<td>Decayed or filled 4</td>
</tr>
<tr>
<td>United States (Eklund et al. 1987)</td>
<td>27-65</td>
<td>Molars</td>
<td>38</td>
<td>Mild to moderate</td>
<td>Decayed, missing or filled 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>Severe</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Premolars</td>
<td>38</td>
<td>Mild to moderate</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>Severe</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior</td>
<td>38</td>
<td>Mild to moderate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>Severe</td>
<td>6</td>
</tr>
</tbody>
</table>

Percentage of decayed, missing and filled teeth. Not all researchers reported P-values for the specific contrasts in these tables. Moreover, the results are not independent, as some researchers studied more than one age group or reported results for more than one caries frequency measure or for more than one type of teeth. Nevertheless, in 11 of the 14 available contrasts, the measure of caries frequency was higher among those with severe fluorosis than among those with mild to moderate forms. In some comparisons, the differences were slight. Descriptively, the most pronounced differences were for all teeth among children age 15-16 years in Israel (Mann et al. 1987, Table 4-7), for all teeth among children age 8-16 years in Illinois (Driscoll et al. 1986, Table 4-9), for premolars among adults age 27-65 in New Mexico (Eklund et al. 1987, Table 4-9), and for all teeth among children ages 6-7 and 13-14 in Ethiopia (Olsson 1979, Table 4-9).

Mixed evidence comes from correlation or regression analyses. In studies in Uganda (Rwenyonyi et al. 2001) and Tanzania (Awadia et al. 2002), statistically significant correlations were not observed (P > 0.05) between severe fluorosis and caries frequency. A study of children in a South African community with a water fluoride concentration of 3 mg/L and a 30% prevalence of severe fluorosis reported a positive correlation (P < 0.05) between fluorosis scores on the Dean index and caries experience (DMFT) (Grobler et al. 2001). In the same study, no correlation between fluorosis and caries.
frequency was found in two other communities with water fluoride concentrations of 0.5 and 0.2 mg/L, in which the prevalence of severe fluorosis was 1% and 0%, respectively.

The studies on severe enamel fluorosis and caries are limited by being cross-sectional in design and conducted in a wide range locales. In most of the studies, there was no adjustment for oral hygiene, dental care, or other determinants of caries risk. Moreover, as previously noted, measures of the role of chance (i.e., confidence intervals or P-values) are not available for the specific contrasts of interest to the present report. Nevertheless, the hypothesis of a causal link between severe enamel fluorosis and increased caries risk is plausible and the evidence is mixed but supportive.

OTHER DENTAL EFFECTS

Fluoride may affect tooth dentin as well as enamel. The patterns of change observed in bone with age also occur in dentin, a collagen-based mineralized tissue underlying tooth enamel. Dentin continues to grow in terms of overall mass and mineral density as pulp cells deposit more matrix overall and more mineral in the dentin tubules. Several investigators have observed that, like older bone, older dentin is less resistant to fracture and tends to crack more easily (Arola and Repproge 2005; Imbeni et al. 2005; Wang 2005). Aged dentin tends to be hypermineralized and sclerotic, where the dentin tubules have been filled with mineral and the apatite crystals are slightly smaller (Kinney et al. 2005), which could be significant because, as dentin ages in the presence of high amounts of fluoride, the highly packed fluoride-rich crystals might alter the mechanical properties of dentin as they do in bone (see Chapter 5). Unlike bone, however, dentin does not undergo turnover. Some preliminary studies show that fluoride in dentin can even exceed concentrations in bone and enamel (Mukai et al. 1994; Cutress et al. 1996; Kato et al. 1997; Sapov et al. 1999; Vieira et al. 2004). Enamel fluorosis, which accompanies elevated intakes of fluoride during periods of tooth development, results not only in enamel changes as discussed above but also in dentin changes. It has now been well established that fluoride is elevated in fluorotic dentin (Mukai et al. 1994; Cutress et al. 1996; Kato et al. 1997; Sapov et al. 1999; Vieira et al. 2004). Whether excess fluoride incorporation in fluorotic teeth increases the risk for dentin fracture remains to be determined, but the possibility cannot be ruled out.

Questions have also been raised about the possibility that fluoride may delay eruption of permanent teeth (Kunzel 1976; Virtanen et al. 1994; Leroy et al. 2003). The hypothesized mechanisms for this effect include prolonged retention of primary teeth due to caries prevention and thickening of the bone around the emerging teeth (Kunzel 1976). However, no systematic studies of tooth eruption have been carried out in communities exposed
to fluoride at 2 to 4 mg/L in drinking water. Delayed tooth eruption could affect caries scoring for different age groups.

FINDINGS

One of the functions of tooth enamel is to protect the dentin and, ultimately, the pulp from decay and infection. Severe enamel fluorosis compromises this health-protective function by causing structural damage to the tooth. The damage to teeth caused by severe enamel fluorosis is a toxic effect that the majority of the committee judged to be consistent with prevailing risk assessment definitions of adverse health effects. This view is consistent with the clinical practice of filling enamel pits in patients with severe enamel fluorosis and restoring the affected teeth.

In previous reports, all forms of enamel fluorosis, including the severest form, have been judged to be aesthetically displeasing but not adverse to health (EPA 1986; PHS 1991; IOM 1997; ADA 2005). This view has been based largely on the absence of direct evidence that severe enamel fluorosis results in tooth loss, loss of tooth function, or psychological, behavioral, or social problems. The majority of the present committee finds the rationale for considering severe enamel fluorosis only a cosmetic effect much weaker for discrete and confluent pitting, which constitutes enamel loss, than it is for the dark yellow to brown staining that is the other criterion symptom of severe fluorosis. Moreover, the plausible hypothesis of elevated caries frequency in persons with severe enamel fluorosis has been accepted by some authorities and has a degree of support that, though not overwhelmingly compelling, is sufficient to warrant concern. The literature on psychological, behavioral, and social effects of enamel fluorosis remains quite meager. None of it focuses specifically on the severe form of the condition or on parents of affected children or on affected persons beyond childhood.

Two of the 12 members of the committee did not agree that severe enamel fluorosis should now be considered an adverse health effect. They agreed that it is an adverse dental effect but found that no new evidence has emerged to suggest a link between severe enamel fluorosis, as experienced in the United States, and a person’s ability to function. They judged that demonstration of enamel defects alone from fluorosis is not sufficient to change the prevailing opinion that severe enamel fluorosis is an adverse cosmetic effect. Despite their disagreement on characterization of the condition, these two members concurred with the committee’s conclusion that the MCLG should prevent the occurrence of this unwanted condition.

Severe enamel fluorosis occurs at an appreciable frequency, approximately 10% on average, among children in U.S. communities with water fluoride concentrations at or near the current MCLG of 4 mg/L. Strong evidence exists of an approximate population threshold in the United States,
such that the prevalence of severe enamel fluorosis would be reduced to nearly zero by bringing the water fluoride levels in these communities down to below 2 mg/L. There is no strong and consistent evidence that an appreciable increase in caries frequency would occur by reducing water fluoride concentrations from 4 mg/L to 2 mg/L or lower. At a fluoride concentration of 2 mg/L, severe enamel fluorosis would be expected to become exceedingly rare, but not be completely eradicated. Occasional cases would still arise for reasons such as excessive fluoride ingestion (e.g., toothpaste swallowing), inadvisable use of fluoride supplements, and misdiagnosis.

Despite the characterization of all forms of enamel fluorosis as cosmetic effects by previous groups, there has been general agreement among them, as well as in the scientific literature, that severe and even moderate enamel fluorosis should be prevented. The present committee’s consensus finding that the MCLG should be set to protect against severe enamel fluorosis is in close agreement with conclusions by the Institute of Medicine (IOM 1997), endorsed recently by the American Dental Association (ADA 2005). As shown in Table 4-10, between 25% and 50% of U.S. children in communities with drinking water containing fluoride at 4 mg/L would be expected to consume more than the age-specific tolerable upper limits of fluoride intake set by IOM. Results from the Iowa Fluoride Study (Levy 2003) indicate that even at water fluoride levels of 2 mg/L and lower, some children’s fluoride intake from water exceeds the IOM’s age-specific tolerable upper limits (Table 4-11).

For all age groups listed in Table 4-10, the IOM’s tolerable upper intake values correspond to a fluoride intake of 0.10 mg/kg/day (based on default body weights for each age group; see Appendix B). Thus, the exposure estimates in Chapter 2 also showed that the IOM limits would be exceeded at 2 mg/L for nonnursing infants at the average water intake level (Table 2-14). Specifically, as described in Chapter 2 (Tables 2-14 and 2-15), nonnursing

<table>
<thead>
<tr>
<th>TABLE 4-10 Tolerable Upper Fluoride Intakes and Percentiles of the U.S. Water Intake Distribution, by Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
</tr>
<tr>
<td>Fluoride, mg/day</td>
</tr>
<tr>
<td>0-6 months</td>
</tr>
<tr>
<td>7-12 months</td>
</tr>
<tr>
<td>1-3 years</td>
</tr>
<tr>
<td>4-8 years</td>
</tr>
</tbody>
</table>

Ages 4-6 years. For ages 7-10 years, the 50th percentile is 355 mL/day and the 75th percentile is 669 mL/day.
infants have an average total fluoride intake (all sources except fluoride supplements) of 0.144 and 0.258 mg/kg/day at 2 and 4 mg/L fluoride in drinking water, respectively. Corresponding values are 0.090 and 0.137 mg/kg/day for children 1-2 years old and 0.082 and 0.126 mg/kg/day for children 3-5 years old. Furthermore, at EPA’s current default drinking water intake rate, the exposure of infants (nursing and non-nursing) and children 1-2 years old would be at or above the IOM limits at a fluoride concentration of 1 mg/L (Table 2-13). For children with certain medical conditions associated with high water intake, estimated fluoride intakes from all sources (excluding fluoride supplements) range from 0.13-0.18 mg/kg/day at 1 mg/L to 0.23-0.33 mg/kg/day at 2 mg/L and 0.43-0.63 mg/kg/day at 4 mg/L.

IOM’s tolerable upper limits were established to reduce the prevalence not only of severe fluorosis, but of moderate fluorosis as well, both of which ADA (2005) describes as unwanted effects. The present committee, in contrast, focuses specifically on severe enamel fluorosis and finds that it would be almost eliminated by a reduction of water fluoride concentrations in the United States to below 2 mg/L. Despite this difference in focus, the committee’s conclusions and recommendations with regard to protecting children from enamel fluorosis are squarely in line with those of IOM and ADA.

The current SMCL of 2 mg/L is based on a determination by EPA that objectionable enamel fluorosis in a significant portion of the population is an adverse cosmetic effect. EPA defined objectionable enamel fluorosis as discoloration and/or pitting of teeth. As noted above, the majority of the committee concludes it is no longer appropriate to characterize enamel pitting as a cosmetic effect. Thus, the basis of the SMCL should be discoloration of tooth surfaces only.

The prevalence of severe enamel fluorosis is very low (near zero) at fluoride concentrations below 2 mg/L. However, from a cosmetic stand-

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**TABLE 4-11** Comparison of Intakes from Drinking Water\(^a\) from the Iowa Fluoride Study and IOM’s Upper Tolerable Intakes

<table>
<thead>
<tr>
<th>Age, months</th>
<th>IOM Tolerable Upper Intake (mg/day)</th>
<th>Percentiles of Iowa Fluoride Study Distribution (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>75th</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>24</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>36</td>
<td>1.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^a\)Fluoride concentrations in drinking water ranged from <0.3 to 2 mg/L.

point, the SMCL does not completely prevent the occurrence of moderate enamel fluorosis. EPA has indicated that the SMCL was intended to reduce the severity and occurrence of the condition to 15% or less of the exposed population. No new studies of the prevalence of moderate enamel fluorosis in U.S. populations are available. Past evidence indicated an incidence range of 4% to 15% (50 Fed. Reg. 20164 [1985]). The prevalence of moderate cases that would be classified as being of aesthetic concern (discoloration of the front teeth) is not known but would be lower than 15%. The degree to which moderate enamel fluorosis might go beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is also not known.

RECOMMENDATIONS

- Additional studies, including longitudinal studies, of the prevalence and severity of enamel fluorosis should be done in U.S. communities with fluoride concentrations higher than 1 mg/L. These studies should focus on moderate and severe enamel fluorosis in relation to caries and in relation to psychological, behavioral, and social effects among affected children, their parents, and affected children after they become adults.
- Methods should be developed and validated to objectively assess enamel fluorosis. Consideration should be given to distinguishing between staining or mottling of the anterior teeth and of the posterior teeth so that aesthetic consequences can be more easily assessed.
- More research is needed on the relation between fluoride exposure and dentin fluorosis and delayed tooth eruption patterns.
Musculoskeletal Effects

This chapter evaluates the effects of fluoride exposure on the musculoskeletal system. Topics considered include the effects of fluoride on bone cells (both bone-forming and bone-resorbing cells), on the developing growth plate, and on articular cartilage as it may relate to arthritic changes. New data on the effects of fluoride on skeletal architecture, bone quality, and bone fracture are also considered. Information on bone cancer is provided in Chapter 10. Effects on tooth development and other issues of oral biology are discussed in Chapter 4.

CHEMISTRY OF FLUORIDE AS IT RELATES TO MINERALIZING TISSUES

Fluoride is the ionic form of the element fluorine. Greater than 99% of the fluoride in the body of mammals resides within bone, where it exists in two general forms. The first is a rapidly exchangeable form that associates with the surfaces of the hydroxyapatite crystals of the mineralized component of bone. Fluoride in this form may be readily available to move from a bone compartment to extracellular fluid. Bone resorption is not necessary for the release of fluoride in this form. However, the predominant form of fluoride in bone resides within the hydroxyapatite crystalline matrix.

Hydroxyapatite is the mature form of a calcium phosphate insoluble salt that is deposited in and around the collagen fibrils of skeletal tissues. The formula for pure hydroxyapatite is $\text{Ca}_{10}\text{(PO}_4\text{)}_6\text{OH}_2$. It results from the maturation of initial precipitations of calcium and phosphate during the mineralization process. As the precipitate matures, it organizes into...
hexagonal, terraced hydroxyapatite crystals. Recent analysis of bone mineral indicates that a significant proportion of the hydroxyapatite crystal is a form of carbonated apatite, where carbonyl groups \((\text{CO}_3^-)\) replace some of the \(\text{OH}^-\) groups. Carbonated apatite is more soluble than hydroxyapatite at acid pH. Fluoride incorporation into the crystalline structure of bone mineral occurs with the creation of a form of apatite known as fluoroapatite (or fluorapatite). The formula for this form of the crystal is \(\text{Ca}_{10} (\text{PO}_4)_6 \text{F}_2\) or \(\text{Ca}_{10} (\text{PO}_4)_6 \text{OHF}\). These crystals also take on a hexagonal shape and are found in terraced layers but, depending on the extent of fluoride in the crystal, may be somewhat more elongated than pure hydroxyapatite. Because fluoroapatite is less soluble in acidic solutions than hydroxyapatite, it was expected that fluoride incorporation into bone might actually make the tissue stronger. However, this has proven not to be the case in human studies (see below).

Release of fluoride from bone when it is in the form of fluoroapatite requires osteoclastic bone resorption. Acidification of the mineral matrix by the osteoclast is sufficient to solubilize the fluoroapatite and allow free exchange with extracellular fluids. Once released, the effect of fluoride on bone cells may be evident; however, the form in which fluoride has its effect remains under debate. Some investigators contend that fluoride directly affects bone cells, but others claim that the effect must be mediated by fluoride while in a complex with aluminum.

Do fluoroaluminate complexes exist in biological fluids? The answer to this question depends in large part on pH, protein concentration, and cell composition. However, in general, in the acid environment of the stomach much of the aluminum and fluoride exist in a complex of \(\text{AlF}_3\) or \(\text{AlF}_4^-\). These forms (mostly \(\text{AlF}_3\)) have been purported to cross the intestine and enter cells (Powell and Thompson 1993). Once inside a bone cell the \(\text{AlF}_x\) form appears to activate a specific protein tyrosine kinase through a \(\text{G}\) protein and evoke downstream signals. A more complete discussion of this process is presented in a later section of this chapter.

The prolonged maintenance of fluoride in the bone requires that uptake of the element occurs at the same or greater rate than its clearance. This appears to be the case. (See Chapter 3 for more detailed discussion of the pharmacokinetic data on fluoride.) Turner et al. (1993) put forward a mathematical model that appears to fit the known pharmacokinetic data. This model assumes that fluoride influx into bone is a nonlinear function. This assumption is supported by pharmacokinetic data (Ekstrand et al. 1978; Kekki et al. 1982; Ekstrand and Spak 1990) and is required for the model to accurately predict fluoride movements. Another reasonable assumption is that the bulk of fluoride that moves between the skeleton and the extracellular fluid is due to bone remodeling. That is, most of the fluoride is either influxing or effluxing as a result of cellular activity. The outcome of the
Turner model predicts that (1) fluoride uptake is positively associated with the bone remodeling rate and (2) fluoride clearance from the skeleton takes at least four times longer than fluoride uptake. A key correlate to the first prediction is that the concentration of fluoride in bone does not decrease with reduced remodeling rates. Thus, it appears that fluoride enters the bone compartment easily, correlating with bone cell activity, but that it leaves the bone compartment slowly. The model assumes that efflux occurs by bone remodeling and that resorption is reduced at high concentrations of fluoride because of hydroxyapatite solubility. Hence, it is reasonable that 99% of the fluoride in humans resides in bone and the whole body half-life, once in bone, is approximately 20 years (see Chapter 3 for more discussion of pharmacokinetic models).

The effects of fluoride on bone quality are evident but are less well characterized than its effects on bone cells. Bone quality is an encompassing term that may mean different things to different investigators. However, in general it is a description of the material properties of the skeleton that are unrelated to skeletal density. In other words, bone quality is a measure of the strength of the tissue regardless of the mass of the specimen being tested. It includes parameters such as extent of mineralization, microarchitecture, protein composition, collagen cross linking, crystal size, crystal composition, sound transmission properties, ash content, and remodeling rate. It has been known for many years that fluoride exposure can change bone quality. Franke et al. (1975) published a study indicating that industrial fluoride exposure altered hydroxyapatite crystal size and shape. Although the measurements in their report were made with relatively crude x-ray diffraction analyses, they showed a shorter and more slender crystal in subjects who were aluminum workers and known to be exposed to high concentrations of fluoride. Other reports documenting the effects of fluoride on ultrasound velocities in bone, vertebral body strength, ash content, and stiffness have shown variable results (Lees and Hanson 1992; Antich et al. 1993; Richards et al. 1994; Zerwekh et al. 1997a; Søgaard et al. 1994, 1995, 1997); however, the general conclusion is that, although there may be an increase in skeletal density, there is no consistent increase in bone strength. A carefully performed comparison study between the effects of fluoride (2 mg/kg/day) and alendronate in minipigs likely points to the true effect: “in bone with higher volume, there was less strength per unit volume, that is, . . . there was a deterioration in bone quality” (Lafage et al. 1995).

**EFFECT OF FLUORIDE ON CELL FUNCTION**

Two key cell types are responsible for bone formation and bone resorption, the osteoblast and osteoclast, respectively. Osteoprogenitor cells give rise to osteoblasts. Osteoprogenitor cells are a self-renewing population of
cells that are committed to the osteoblast lineage. They originate from mesenchymal stem cells. Osteoblasts contain a single nucleus, line bone surfaces, possess active secretory machinery for matrix proteins, and produce very large amounts of type I collagen. Because they also produce and respond to factors that control bone formation as well as bone resorption, they play a critical role in the regulating skeletal mass. Osteoclasts are giant, multinucleated phagocytic cells that have the capability to erode mineralized bone matrix. They are derived from cells in the monocyte/macrophage lineage. Their characteristic ultrastructural features allow them to resorb bone efficiently by creating an extracellular lysosome where proteolytic enzymes, reactive oxygen species, and large numbers of protons are secreted. Osteoclastogenesis is controlled by local as well as systemic regulators.

**Effect of Fluoride on Osteoblasts**

Perhaps the single clearest effect of fluoride on the skeleton is its stimulation of osteoblast proliferation. The effect on osteoblasts was surmised from clinical trials in the early 1980s documenting an increase in vertebral bone mineral density that could not be ascribed to any effect of fluoride on bone resorption. Biopsy specimens confirmed the effect of fluoride on increasing osteoblast number in humans (Briancon and Meunier 1981; Harrison et al. 1981). Because fluoride stimulates osteoblast proliferation, there is a theoretical risk that it might induce a malignant change in the expanding cell population. This has raised concerns that fluoride exposure might be an independent risk factor for new osteosarcomas (see Chapter 10 for the committee’s assessment).

The demonstration of an effect of fluoride on osteoblast growth in vitro was first reported in 1983 in avian osteoblasts (Farley et al. 1983). This study showed that fluoride stimulated osteoblast proliferation in a biphasic fashion with the optimal mitogenic concentration being 10 µM. The finding that fluoride displayed a biphasic pattern of stimulation (achieving a maximal effect at a specific concentration and declining from there) suggests that multiple pathways might be activated. It is possible that low, subtoxic doses do stimulate proliferation, but at higher doses other pathways responsible for decreasing proliferation or increasing apoptosis might become activated. This thinking suggested that fluoride might have multiple effects on osteoblasts and that might be the reason for some paradoxical findings in the clinical literature (see below). Nevertheless, the characteristics of the fluoride effect point clearly to a direct skeletal effect. Some of these characteristics are as follows: (1) the effects of fluoride on osteoblasts occur at low concentrations in vivo and in vitro (Lau and Baylink 1998); (2) fluoride effects are, for the most part, skeletal specific (Farley et al. 1983; Wergedal et al. 1988); (3) fluoride effects may require the presence of a bone-active
growth factor (such as insulin-like-growth factor I or transforming growth factor β) for its action (Farley et al. 1988; Reed et al. 1993); and (4) fluoride affects predominantly osteoprogenitor cells as opposed to mature functioning osteoblasts (Bellows et al. 1990; Kassem et al. 1994).

Understanding the subcellular signaling mechanisms by which fluoride affects osteoblasts is of paramount importance. Information in this area has the potential to determine whether the fluoride effects are specific, whether toxicity is an issue, and what concentration may influence bone cell function. Moreover, as the pathways become more clearly defined, other targets might emerge. Two hypotheses in the literature describe the effect of fluoride. Both state that the concentration of tyrosine phosphorylated signal pathway intermediates is elevated after fluoride exposure. However, the means by which this occurs differs in the hypotheses. One view is that fluoride blocks or inhibits the activity of a phosphotyrosine phosphatase, thereby increasing the pool of tyrosine-phosphorylated proteins. The other view supports an action of fluoride (along with aluminum) on the stimulation of tyrosine phosphorylation that would also increase the pool of tyrosine-phosphorylated proteins. In the first hypothesis, growth factor activation of the Ras-Raf-MAP kinase pathway would involve stimulation of phosphotyrosine kinase activity. This is mediated by a family of cytosolic G proteins with guanosine triphosphate acting as the energy source. In the presence of fluoride, a sustained high concentration of tyrosine-phosphorylated proteins would be maintained because of the inability of the cell to dephosphorylate the proteins. This theory implicates the existence of a fluoride-sensitive tyrosine phosphatase in osteoblasts. Such an enzyme has been identified and purified. It appears to be a unique osteoblastic acid phosphatase-like enzyme that is inhibited by clinically relevant concentrations of fluoride (Lau et al. 1985, 1987, 1989; Wergedal and Lau 1992). The second hypothesis supports the belief that an AlFx complex activates tyrosine phosphorylation directly. Data from this viewpoint indicate that fluoride alone does not stimulate tyrosine phosphorylation but rather that it requires the presence of aluminum (Caverzasio et al. 1996). The purported mechanism is that the MAP kinase pathway is activated by AlFx, which triggers the proliferation response. A novel tyrosine kinase, Pyk2, has been identified that is known to be activated by AlFx through a G-protein-coupled response and might be responsible for this effect (Jeschke et al. 1998). Two key pieces of evidence that support a G-protein-regulated tyrosine kinase activation step in the fluoride effect are that the mitogenic effect of fluoride can be blocked by genistein (a protein tyrosine kinase inhibitor) and pertussis toxin (a specific inhibitor of heterotrimeric G proteins) (Caverzasio et al. 1997; Susa et al. 1997).

At least two other potential mechanisms deserve mention. Kawase and Suzuki (1989) suggested that fluoride activates protein kinase C (PKC),
and Farley et al. (1993) and Zerwekh et al. (1990) presented evidence that calcium influx into the cells might be a signal for the fluoride-mediated stimulation of proliferation.

In summary, the in vitro effects of fluoride on osteoblast proliferation appear to involve, at the least, a regulation of tyrosine-phosphorylated proteins. Whether this occurs through activation of MAP kinases, G proteins, phosphatases, PKC, or calcium (or a combination) remains to be determined. Whatever the mechanism, however, it is evident that fluoride has an anabolic activity on osteoblasts and their progenitors.

The effects of fluoride on osteoblast number and activity in in vivo studies and clinical trials essentially parallel the in vitro findings. Most reports document increased osteoblast number; however, some investigators have documented a complex and paradoxical effect of fluoride in patients with skeletal fluorosis. Boivin et al. (1989, 1990) reported that, in biopsy bone cores taken from 29 patients with skeletal fluorosis of various etiologies (0.79% ± 0.36% or 7,900 ± 3,600 milligrams per kilogram [mg/kg] of bone ash), there is an apparent increase in the production of osteoblasts with a concomitant increase in a toxic effect of fluoride at the cell level. They provided data to indicate that chronic exposure to fluoride in both endemic and industrially exposed subjects led to an increase in bone volume, an increase in cortical width, and an increase in porosity. However, there was no reduction in cortical bone mass. Osteoid parameters (unmineralized type I collagen) were also significantly increased in fluorotic patients. Interestingly, the fluorotic group had more osteoblasts than the control group, with a very high proportion of quiescent, flattened osteoblasts, but the mineral apposition rate was significantly decreased. It appeared as though the increased numbers of quiescent cells were in a prolonged inactive period. Thus, the conclusion drawn by these investigators was that fluoride exposure increased the birth rate of new osteoblasts, but at high concentrations there was an independent toxic effect on the cells that blocked the full manifestation for the increase in skeletal mass. Boivin et al. used a fluoride-specific electrode for measurements in acidified specimens of human bone. As a point of reference to the above findings, they found that normal control subjects (likely not to have lived in areas with water fluoridation) have mean fluoride content in bone ash (from iliac crest samples) ranging from 0.06% to 0.10% (600 to 1,000 mg/kg); untreated osteoporotic patients range from 0.05% to 0.08% (500 to 800 mg/kg); NaF-treated osteoporotic patients range from 0.24% to 0.67% (2,400 to 6,700 mg/kg) depending on duration of therapy; and skeletal fluorosis patients range from 0.56% to 1.33% (5,600 to 13,300 mg/kg) depending on the source and level of exposure (Boivin et al. 1988). All these ranges are of mean concentrations of fluoride and not individual measurements.
Effect of Fluoride on Osteoclasts

The effects of fluoride on osteoclast activity, and by extension the rate of bone resorption, are less well defined than its effects on osteoblasts. In general, there appears to be good evidence that fluoride decreases osteoclastogenesis and osteoclast activity in in vitro systems; however, its effect in in vivo systems is equivocal. This may be due, in part, to the systemic effects of fluoride in whole animals or humans. A further discussion on this point appears below.

Most reports in the literature studying the effect of fluoride on osteoclast function indicate an inhibition. In fact, the effect might be mediated through G-protein-coupled pathways as in the osteoblast. Moonga et al. (1993) showed that fluoride, in the form of AlF$_4^-$ resulted in a marked concentration-dependent inhibition of bone resorption. In association with this inhibition, they found a marked increase in the secretion of tartrate-resistant acid phosphatase (TRAP). TRAP presumably originated from the osteoclast; however, its function as a secreted enzyme is not known. The fluoride effect was reproduced with cholera toxin, another Gs stimulator. This effect does not appear to be mediated solely by an AlF$_x$ complex because studies using NaF have reported similar findings (Taylor et al. 1989, 1990; Okuda et al. 1990).

Further evidence that fluoride might blunt osteoclastic bone resorption was reported in a study that investigated acid production as a critical feature of osteoclastic function. The pH within osteoclasts can be measured with the proton-sensitive dye acridine orange. Studies in which osteoclasts were observed found that parathyroid hormone induced osteoclast acidity but that calcitonin, cortisol, and NaF all blocked the effect. As acidification of the matrix is required for normal osteoclast function, fluoride, in this case, would act as an inhibitor to bone resorption (Anderson et al. 1986).

The effects of fluoride on bone resorption and osteoclast function in vivo present a complex picture. Some well-controlled animal studies document a decrease in osteoclast (as well as odontoclast) activity. In these studies, rodents and rabbits were exposed to doses of fluoride ranging from clinically relevant to high. Time courses ranged from days to weeks, and the findings indicated a statistically significant decrease in the number and activity of resorbing cells (Faccini 1967; Lindskog et al. 1989; Kameyama et al. 1994). Other studies documented little or no statistically significant effect of fluoride on osteoclast activity (Marie and Hott 1986; Huang 1987). Yet other work that utilized skeletal turnover and remodeling showed an increase in resorption after fluoride therapy (Kragstrup et al. 1984; Snow and Anderson 1986). These studies based their conclusions on the initiation of basic multicellular units (BMUs) and extent of remodeling surface. In the field of skeletal research, it has been accepted that adult bone remodels...
itself through the generation of BMUs. This unit is a temporal description of remodeling starting with osteoclastic bone resorption and progressing through a coupled stimulation of bone formation. All BMU activity, thus, is initiated with the action of an osteoclast. An increase in remodeling surface also implies an increase in BMUs. Snow and Anderson (1986) and Kragstrup et al. (1984) demonstrated an increase in resorption under the influence of fluoride by measuring BMU numbers and remodeling surface, respectively. Because these data were derived from intact in vivo animal models, the investigators could not conclude that the effects of fluoride on osteoclastic bone resorption were direct.

It is interesting that only a single report has appeared that links fluoride exposure to the receptor activator of NF kappaB (RANK) ligand, RANK receptor, or osteoprotegerin (OPG) concentrations. These molecules have recently been characterized as end-stage regulators of osteoclast formation and activity (Lee and Kim 2003). RANK ligand is produced by a variety of cells, with osteoblasts being the most prominent. In its usual form, it is a membrane-associated factor that binds to the RANK receptor on pre-osteoclasts and induces their further differentiation. OPG is a decoy RANK receptor that is an endogenous inhibitor of bone resorption by virtue of its ability to bind RANK ligand. A clinical trial by von Tirpitz et al. (2003) showed that both fluoride and bisphosphonate therapy decreased OPG concentrations. If this were a direct effect of fluoride, one would expect to see an increase in bone resorption. Conversely, if fluoride blocked bone resorption, the decrease in OPG concentrations could be due to a compensatory feedback pathway. Unfortunately, there were not enough histologic or biochemical marker data in this report to determine whether the fluoride effect was direct or indirect.

**EFFECTS OF FLUORIDE ON HUMAN SKELETAL METABOLISM**

**Bone Strength and Fracture**

**Cellular and Molecular Aspects**

Inducing a permanent alteration of skeletal mass in an adult human (or experimental animal) is quite difficult, because bone, as an organ system, possesses an innate mechanism for self-correction. That is, rates of bone formation are controlled, for the most part, by rates of bone resorption. As osteoclastic bone resorption increases or decreases, there is a compensatory increase or decrease in the rate of osteoblastic bone formation. This coupling between the two cell activities was first described by Hattner et al. (1965), and is responsible for the maintenance of a steady-state skeletal mass in adults. These early results indicate that effective management of skeletal...
mass would require controlling both cell processes. However, until recently, the only therapies approved by the U.S. Food and Drug Administration for treating osteoporosis in the United States targeted only osteoclastic bone resorption. They included molecules such as the bisphosphonates, estrogen and its analogs, and calcitonin derivatives. Currently, teraparitide is available as the only approved treatment that acts to stimulate osteoblastic bone formation. Fluoride falls into this category and that is the reason why there was such great interest in this ion as a potential therapy for osteoporosis. Unfortunately, fluoride did not prove to be an effective treatment for two major reasons. First, although it showed robust stimulation of bone mineral density (see below), its effects as an agent to reduce fractures have never been unequivocally documented. Second, because this naturally occurring element cannot be protected with a patent, the pharmaceutical industry has not been interested in investigating all its potential.

The first clinical trials of fluoride in humans were performed by Rich and Ensinck (1961). Since then many hundreds of reports have appeared in the medical literature. The overwhelming weight of evidence in these reports documents the effect of fluoride, at therapeutic doses, to be that of an increase in bone mineral density. The lowest dose of NaF to show a clear increase in bone mineral density was 30 mg/day, although there may be effects at lower doses (Hansson and Roos 1987; Kleerekoper and Balena 1991). Response was linear with time for at least 4 to 6 years (Riggs et al. 1990). This linear relationship was confirmed in another study lasting more than 10 years (Kleerekoper and Balena 1991). The observation that bone mineral density continues to increase with time is not surprising in and of itself; however, it differs from the action of the antiresorptive bisphosphonates. Whereas agents that depress bone resorption are most effective when the rate of bone remodeling is high, there appears to be no relationship between the rate of remodeling and the response to fluoride. Also, in contrast to the recent data demonstrating a persistence of bone density with the discontinuance of bisphosphonate therapy, discontinuance of fluoride therapy leads to immediate resumption of bone density loss (Talbot et al. 1996).

The dose and duration of fluoride exposure are critical components in determining the effects of the ingested ion on bone. In addition, approximately 30% of patients do not respond to fluoride at any dose (Kleerekoper and Mendlovic 1993). Moreover, there are wide variations in bioavailability among patients and fluoride preparations, and individual responses to the ion also vary widely (Boivin et al. 1993; Erlacher et al. 1995). Whereas the daily dose of fluoride in randomized therapeutic trials (20 to 34 mg/day) exceeds that for people drinking water with fluoride at 4 mg/L (4 to 8 mg/day for 1 to 2 L/day), the latter may be exposed much longer, leading to comparable or higher cumulative doses and bone fluoride concentrations (see discussion later in this chapter.)
Allolio and Lehmann (1999) noted that the peak blood concentrations of fluoride after swallowing 8 oz of water (at 1.0 µg/L) all at once will reach 8.75 µg/L. If peak blood concentrations are proportional to water concentration, then consumption of 8 oz of water containing fluoride at 4 mg/L would produce peak concentrations below the threshold for effects on osteoblasts examined in vitro (95 ng/mL) (Ekstrand and Spak 1990). Assuming that the blood fluoride concentrations decline between each episode of water consumption of 8 oz or less, such exposures may not achieve a concentration of fluoride in the extracellular fluids sufficient to affect bone cells. A caveat to this analysis is that bone cells may be exposed to potentially higher (but unknown) concentrations because of their proximity to the mineralized bone compartment. There have been no direct measurements of the local fluoride concentration around a site of bone resorption. However, a calculation based on estimated rates of resorption, diffusion kinetics, and starting concentration indicates that bone cells and other cells in the immediate vicinity may experience high concentrations of fluoride.

The conditions for an estimate of the fluoride concentration as a function of distance from the osteoclast are as follows:

1. The bone being resorbed has a fluoride content of 3,000 mg per kg of bone ash.
2. Bone ash is assumed to include 65% of the volume of viable bone and the density of viable bone is 1.2 g/cm³. Thus, the concentration of fluoride in the bone compartment is approximately 5,500 µg/cm³.
3. An osteoclast resorbs bone at an average rate of about 30,000 µm³ in 2.5 weeks.
4. The osteoclast is delivering fluoride to the extracellular fluid space from a point source with a radius of 20 µm.
5. Diffusion occurs into a three-dimensional spherical space around the osteoclast.
6. The diffusion coefficient of fluoride in extracellular fluid is approximately 1.5 × 10⁻⁵ cm²/s.

Under these conditions, the following equation describes the concentration of fluoride as a function of time and distance from the site of bone resorption (Saltzman 2004):

\[ C_{(r,t)} = \frac{SA}{2Dr} \sqrt{\frac{4Dt}{\pi}} \]

where C is the concentration of fluoride as a function of distance and time, S is the delivery rate of fluoride from the resorption site, A is the radius of the point source from which the fluoride is delivered, D is the diffusion
coefficient of the fluoride, r is the distance from the resorption site, and t is the time after commencement of the resorption. A graphical representation of this function is presented in Figure 5-1.

An examination of the curves in Figure 5-1 indicates that the fluoride concentration around a site of bone resorption can be quite high immediately adjacent to the osteoclast. The theoretical maximum concentration at 20 µm from the site (at the surface of the osteoclast) would be about 5,500 µg/cm³. The concentration rapidly decays to zero in very short times at distances greater than 100 µm from the site. However, it appears that a sustained fluoride concentration is achieved in the range of hours and persists for the entire resorption process. Thus, by 2.5 weeks, the concentration of fluoride will be about 500 µg/cm³ at a distance of 250 µm from the resorption site.

FIGURE 5-1 Concentration of fluoride plotted as a function of time and distance from the site of bone resorption. Release of fluoride from a site of bone resorption can achieve a near steady state concentration in a matter of hours. Twenty microns was defined as the radius of the point source from which fluoride was delivered to the extracellular fluid. Acknowledgement: Hani Awad, University of Rochester, Rochester, New York, assisted in this analysis.
The concentration of fluoride tends toward zero at longer distances. This modeling does not take into account any dissipation of fluoride due to flow of extracellular fluid through the bone marrow compartment. A more complete picture of the local concentration of fluoride around a resorption site should include this factor; however, there are no data on which to base this estimate. Thus, considering that within approximately 1 hour, the fluoride concentration achieves an equilibrium in the surrounding volume, it is likely that the actual fluoride concentration is less, but not substantially so.

Within 250 µm of a site of resorption, it is possible to encounter progenitor cells that give rise to bone, blood, and fat. Thus, one must assume that these cells would be exposed to high concentrations of fluoride. At this time, it is not possible to predict what effect this exposure would have on the functioning of skeletal elements, hematopoiesis, and adipose formation. It should also be pointed out that the number of resoring sites in an adult skeleton at any point in time is quite small, on the order of 1 × 10⁶ sites. That is, of the vast surface area of trabecular bone in a human skeleton, only about 1 million sites of bone resorption are occurring at any given moment. Whether these elevated concentrations of fluoride have a meaningful effect on bone metabolism can only be speculated at this time.

Some studies have measured the fluoride content of bone, but its effect on a direct measurement of bone strength in humans is not easy to determine. Animal studies have provided some clues. Some studies have reported a biphasic effect of fluoride on bone strength (Beary 1969; Rich and Feist 1970; Turner et al. 1992). For example, Turner et al. (1992) reported an increase in bone strength in rats with bone fluoride concentrations up to 1,200 mg/kg, but they found a decrease in strength back to that of untreated animals with concentrations around 6,000 to 7,000 mg/kg. Skeletal specimens with fluoride concentrations greater than this appeared to have less strength than control treated bone. A variable that may affect the analysis of bone strength is the age of the animal (see Chapter 3). Turner et al. (1995) performed another study in which they found little effect of fluoride on bone strength at any concentration in young rats but a significant effect in old rats. The predominant effect in the older animals clustered around bone fluoride concentrations of 6,000 to 8,000 mg/kg (Turner et al. 1995). Thus, whether fluoride has a biphasic effect on bone strength has not been firmly established.

Other reports in the literature suggesting that fluoride might diminish bone strength in animal models have appeared. Studies of rabbits by Turner et al. (1997) and Chachra et al. (1999) have put forward the point of view that fluoride exposure might decrease strength by altering the structural integrity of the bone microarchitecture. Turner et al. (1997) found no effects of fluoride on a number of bone serum markers, but an increase in bone formation and bone mass. However, this was accompanied by a decrease in

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bone strength at multiple sites. In a subsequent paper, these authors suggest that the decrease in strength might be due to alterations in mineral crystal structure (Chachra et al. 1999). Whether these results occur in humans remains to be shown. A decrease in bone strength in a human population will definitely increase the risk of fracture and there have been case reports to document this, especially in subjects who may be highly susceptible to accumulating fluoride, such as those with renal failure (Gerster et al. 1983). A more complete discussion of the effects of fluoride in larger population studies follows.

The applicability of rat studies to quantitatively assess risk of bone fracture in humans is uncertain because of the physiological differences between the skeletons of the species. For example, fluoride uptake into bone occurs more readily in humans than in rats (see Chapter 3 and Appendix D). Rats do not undergo Haversian remodeling in their cortical bones as humans do. On the other hand, if fluoride affects bone properties through crystal structure and the mineral-collagen interface, changes in rat bone strength may provide a model for human bone strength (Turner et al. 1992). In addition, whereas the relationship between bone strength and fracture has been studied in rodents, no comparable data are available for humans. The committee therefore judges that the rat experiments provide qualitative support for an effect of fluoride on fractures in humans but cannot yet be used to make quantitative risk estimates for this end point.

The qualifications noted above for rats do not apply as strongly to the rabbit model. Rabbits undergo Haversian remodeling (i.e., osteoclast bone resorption within cortical bone) as do humans (T. Hirano et al. 1999), and the rabbit growth plate behaves more like a human than does a rat or mouse (Zaleske et al. 1982; Irie et al. 2005). Thus, the rabbit is a better model for studying bone effects than rats or mice.

Epidemiology Data

The committee reviewed epidemiologic data on the relationship between fluoride exposure and fractures from two sources: observational studies of exposure to fluoride in water and randomized clinical trials of the use of fluoride in treating osteoporosis. Table 5-1 summarizes studies of bone fracture in populations exposed to fluoride in drinking water. Most of these studies have compared fluoridated (1 mg/L) and nonfluoridated areas. A meta-analysis by McDonagh et al. (2000a, b) evaluated bone fractures in relation to water fluoridation. Consequently, they excluded data from areas with drinking water fluoridated above 1 mg/L, if data at 1 mg/L were available. Results for fractures were reported as evenly distributed around the null—no effect—but statistical testing showed significant heterogeneity among studies. Because the exposures evaluated in this paper did not spe-
### TABLE 5-1 Studies on Bone Fracture in Populations Exposed to Fluoride in Drinking Water

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Country</th>
<th>Subjects</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecologic</td>
<td>USA</td>
<td>Residents of fluoridated and nonfluoridated communities (age ≥ 65; n (fluoridated communities) = 40 million; n (nonfluoridated communities) = 30 million; n (cases) = 218,951)</td>
<td>Fluoridated Nonfluoridated (concentrations not specified)</td>
</tr>
<tr>
<td>Ecologic</td>
<td>USA</td>
<td>Patients discharged with hip fracture in counties throughout the USA (n = 541,985)</td>
<td>Fluoridated Nonfluoridated (concentrations not specified)</td>
</tr>
<tr>
<td>Ecologic</td>
<td>USA</td>
<td>5% of Medicare population (ages 65 to 89; n [cases] = 59,383)</td>
<td>≤0.3 mg/L (natural) ≥0.7 mg/L (natural and artificial)</td>
</tr>
<tr>
<td>Ecologic</td>
<td>USA</td>
<td>Data from National Health Interview Surveys (ages ≥ 45; n = 44,031)</td>
<td>≥0.7 mg/L (natural); groups assessed in terms of &lt;20% or ≥80% of the population exposed to fluoridated water</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>USA (Oregon, Minnesota, Maryland, Pennsylvania)</td>
<td>Women (ages ≥ 65; n = 5,781)</td>
<td>Exposed to fluoridated or nonfluoridated (concentrations not specified) water for 20 years</td>
</tr>
<tr>
<td>Ecologic</td>
<td>USA</td>
<td>Participants in another epidemiology project (ages ≥ 50)</td>
<td>10 years before and 10 years after fluoridation (1.1 mg/L) was implemented</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>USA (Pennsylvania)</td>
<td>Women participating in osteoporotic fracture study (ages ≥ 65; n = 2,076)</td>
<td>1.0 mg/L (artificial) 0.15 mg/L (natural) Number of years of exposure: 0, 1 to 10, 11 to 20, &gt; 20 years</td>
</tr>
<tr>
<td>Ecologic</td>
<td>USA (Utah)</td>
<td>Hip fracture patients (ages ≥ 65; n = 246)</td>
<td>1 mg/L (artificial) &lt;0.3 mg/L (natural)</td>
</tr>
</tbody>
</table>
**MUSCULOSKELETAL EFFECTS**

<table>
<thead>
<tr>
<th>Observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk (RR) of hip fracture in fluoridated communities was 1.08 (95% confidence interval [CI] 1.06 to 1.10) for women and 1.17 (95% CI 1.13 to 1.22) for men.</td>
<td>Jacobsen et al. 1992</td>
</tr>
<tr>
<td>Lack of dose-response relationship between hip fracture risk and duration of water fluoridation. Analyses of annual age-adjusted incidence rates by duration of county water fluoridation showed a pattern of lowest risk in nonfluoridated counties and highest risk in counties fluoridated for up to 5 years, but rates gradually declined for longer durations.</td>
<td></td>
</tr>
<tr>
<td>Weak positive association (before and after adjustment) between hip fracture incidence and percent of county residents who live in counties with fluoridated water.</td>
<td>Jacobsen et al. 1990</td>
</tr>
<tr>
<td>RR of hip fracture in the fluoridated group was 1.00 (95% CI 0.92 to 1.09) for men and 1.01 (95% CI 0.96 to 1.06) for women. For ankle fracture, it was 1.01 (95% CI 0.87 to 1.16) for men and 1.00 (95% CI 0.92 to 1.08) for women. For fractures of the distal forearm and proximal humerus, a gender difference in risk was found. For women, there was no association between fluoridation and the two types of fractures. Men in fluoridated areas had a 23% higher risk of proximal humerus fracture (RR 1.23; 95% CI 1.06 to 1.43) and a 16% higher risk of distal forearm fracture (RR 1.16; 95% CI .02 to 1.33). Rate of hip fracture hospitalization per 1,000 in the population with &lt;20% exposed was 2.4 for women and 1.0 for men. For the group with ≥80% exposed, the rates were 2.2 for women and 1.1 for men.</td>
<td>Karagas et al. 1996</td>
</tr>
<tr>
<td>RR after multivariate adjustment was 0.96 (95% CI 0.83 to 1.10; P = 0.536) for nonvertebral fractures, 0.73 (95% CI 0.55 to 0.97; P = 0.033) for vertebral fractures, 0.69 (95% CI 0.50 to 0.96; P = 0.028) for hip fractures, 0.85 (95% CI 0.58 to 1.23; P = 0.378) for humerus fractures, and 1.32 (95% CI 1.00 to 1.71; P = 0.051) for wrist fractures.</td>
<td>Phipps et al. 2000</td>
</tr>
<tr>
<td>Incidence of hip fracture was 484 per 100,000 residents before fluoridation and 450 per 100,000 residents after fluoridation. RR associated with fluoridation was 0.63 (95% CI 0.46 to 0.86). Axial and appendicular bone mass was similar between women exposed to fluoride for &gt;20 years and those exposed for ≤20 years. No significant association was found between fluoride exposure and wrist, spinal, nonspinal, osteoporotic, or hip fractures.</td>
<td>Jacobsen et al. 1993</td>
</tr>
<tr>
<td>RR of hip fracture in the fluoridated population was 1.27 (90% CI 1.08 to 1.46) for women and 1.41 (95% CI 1.00 to 1.81) in men.</td>
<td>Danielsson et al. 1992</td>
</tr>
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<table>
<thead>
<tr>
<th>Study Design</th>
<th>Country</th>
<th>Subjects</th>
<th>Exposure</th>
</tr>
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<tbody>
<tr>
<td>Prospective</td>
<td>USA (Iowa)</td>
<td>Women from three communities with different concentrations of fluoride in water (ages 20-92, n = 1,300)</td>
<td>1 mg/L (w/Ca at 60 mg/L) 1 mg/L (w/Ca at 375 mg/L) 4 mg/L (w/Ca at 15 mg/L)</td>
</tr>
<tr>
<td>cohort</td>
<td>USA (Iowa)</td>
<td>Women from 3 communities with different concentrations of fluoride in water (ages 20-35 and 55-80; n = 158 [referents], n = 230 [high fluoride])</td>
<td>1 mg/L (w/Ca at 67 mg/L) 1 mg/L (w/Ca at 375 mg/L) 4 mg/L (w/Ca at 15 mg/L)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>USA (Iowa)</td>
<td>Women from 3 communities with different concentrations of fluoride in water</td>
<td>1 mg/L (w/Ca at 60 mg/L) 1 mg/L (w/Ca at 375 mg/L) 4 mg/L (w/Ca at 15 mg/L)</td>
</tr>
<tr>
<td>cohort</td>
<td>USA (Michigan)</td>
<td>Female Medicaid recipients (ages ≥ 65)</td>
<td>≥89% of the population receives fluoridated water (2 groups)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;15% of the population receives fluoridated water</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Canada</td>
<td>Patients (ages 45 to 64, 65+) with hip fracture in two cities</td>
<td>0.3 mg/L</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1 mg/L</td>
</tr>
<tr>
<td>Case-control</td>
<td>United Kingdom</td>
<td>Patients with hip fractures (ages ≥ 50; n [cases]) = 514; n [controls]= 527</td>
<td>&lt;0.9 mg/L (artificial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.9 mg/L (natural)</td>
</tr>
<tr>
<td>Ecologic</td>
<td>England, Wales</td>
<td>Patients discharged from hospital after hip fracture (ages ≥ 45; n = 20,393)</td>
<td>0.005 to 0.93 mg/L (natural and artificial)</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>Subjects enrolled in another study (ages ≥ 65; n = 3,216)</td>
<td>0.05 to 0.11 mg/L.</td>
</tr>
<tr>
<td>Prospective</td>
<td>France</td>
<td></td>
<td>0.11 to 0.25 mg/L.</td>
</tr>
<tr>
<td>cohort</td>
<td></td>
<td></td>
<td>&gt;0.25 mg/L</td>
</tr>
<tr>
<td>Ecologic</td>
<td>France</td>
<td>Subjects enrolled in another study on aging (ages ≥ 65; n = 3,777)</td>
<td>0.05 to 0.11 mg/L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.11 to 1.83 mg/L.</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Germany</td>
<td>Residents of fluoridated and nonfluoridated communities</td>
<td>0.08 to 0.36 mg/L (natural)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.77 to 1.20 mg/L (artificial)</td>
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</table>
MUSCULOSKELETAL EFFECTS

Observations

RR for osteoporotic fractures was 2.55 (P = 0.07) in the 4 mg/L group. Serum fluoride concentrations were not related to osteoporotic fractures or bone mineral density.

In the 4-mg/L group, RR of any fracture was 1.81 (95% CI 0.45 to 8.22) in premenopausal women and 2.11 (95% CI 1.01 to 4.43) in postmenopausal women. RR for fractures of the hip, wrist, or spine was 2.70 (95% CI 0.16 to 8.28) in premenopausal women and 2.20 (95% CI 1.07 to 4.69) in postmenopausal women.

Postmenopausal women in the 4 mg/L group reported significantly more fractures than the other two groups.

Long-bone fracture rates were 94.3 per 1,000 and 81.1 per 1,000 in the two populations that are ≥ 89% fluoridated. The rate was 78.8 per 1,000 in the population that was < 15% fluoridated.

For men, ages 45 to 64, standardized hospital admission rates were 0.59 and 0.55, respectively; for men over 65, rates were 5.09 and 4.52. For women, ages 45 to 64, corresponding rates were 0.60 and 0.71; and for ages over 65, they were 9.54 and 9.91.

Estimated average lifetime exposure to fluoride in drinking water ranged from 0.15 to 1.79 mg/L. Odds ratio associated with an average lifetime exposure to ≥ 0.9 mg/L was 1.0 (94% CI 0.7 to 1.5).

Discharge rates ranged from 0.88 to 2.30. No correlation was found between discharge rates for patients with proximal femur fractures and water fluoride concentrations (r = 0.16, P = 0.34). Subsequent reanalysis of the data using a weighted least-squares technique showed a positive correlation between fluoride concentrations and hip fracture (r = 0.41, P = 0.009).

Odds ratio for hip fractures was 1, 3.25 (95% CI 1.66 to 6.38), and 2.43 (95% CI 1.11 to 5.33), respectively. Odds ratio for non-hip fractures was 1, 0.88 (95% CI 0.63 to 1.22), and 1.05 (95% CI 0.74 to 1.51).

Odds ratio for hip fractures were 1 and 1.86 (90% CI 1.02 to 3.36), respectively. Odds ratio for non-hip fractures were 1 and 0.98 (95% CI 0.80 to 1.21), respectively.

Mean annual incidence of hip fracture in the fluoridated community was 173.36 per 100,000 for women and 56.79 per 100,000 men. In the nonfluoridated group, it was 189.35 per 100,000 in women and 56.60 per 100,000 in men.

continued
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Country</th>
<th>Subjects</th>
<th>Exposure</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecologic</td>
<td>Italy</td>
<td>Residents of two counties</td>
<td>1.45 mg/L (natural) 0.05 mg/L (natural)</td>
<td>Significantly greater rate of fracture incidence, particularly femur fractures (RR for males 4.28 and for females 2.64), in the low-exposure community.</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>Finland</td>
<td>Residents of a rural location (n = 144,627)</td>
<td>≤0.1 mg/L 0.11 to 0.30 mg/L (natural) 0.31 to 0.50 mg/L (natural) 0.51 to 1.00 mg/L (natural) 1.10 to 1.50 mg/L (natural) &gt;1.50 mg/L (natural)</td>
<td>Age-and area-adjusted RRs for men were 1.0, 1.05 (95% CI 0.90 to 1.22), 0.72 (95% CI 0.51 to 1.02), 1.03 (95% CI 0.81 to 1.32), 0.67 (95% CI 0.46 to 0.97), and 0.98 (95% CI 0.61 to 1.60). Corresponding values for women were 1.0, 0.93 (95% CI 0.84 to 1.02), 1.12 (95% CI 0.93 to 1.34), 1.12 (95% CI 0.96 to 1.31), 1.08 (95% CI 0.88 to 1.32), and 1.08 (95% CI 0.80 to 1.46). Among women aged 50 to 64 years, fluoride was associated with increased risk of hip fracture. Age- and area-adjusted rate ratio for this age group was 2.09 (95% CI 1.16 to 3.76) in the highest-exposure group (&gt;1.5 mg/L) compared with the lowest-exposure group (≤0.1 mg/L).</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>Finland</td>
<td>Premenopausal women in a province (ages 47 to 56; n = 3,222)</td>
<td>&lt;0.3 mg/L (natural) 1.0 to 1.2 mg/L (artificial) &gt;1.5 mg/L (natural)</td>
<td>No significant difference in fracture incidence among the fluoridated (15.4%) and nonfluoridated group (13.4%) (P = 0.220).</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Finland</td>
<td>Patients with hip fracture (ages ≥ 50)</td>
<td>&lt;0.3 mg/L (natural) 1.0 to 1.2 mg/L (artificial) &gt;1.5 mg/L (natural)</td>
<td>No difference in incidence of hip fracture among exposure groups. Osteofluorosis was found in 22% of the high exposure group. Fluoride content of the bone was correlated with volumetric density of trabecular bone and osteoid-covered trabecular bone surface.</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Finland</td>
<td>Residents in two towns (n = 71,811 and n = 61,587)</td>
<td>&lt;0.1 mg/L 1 mg/L</td>
<td></td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>China</td>
<td>Residents of rural communities exposed to various concentrations of fluoride in drinking water (ages ≥ 50; n = 8,266)</td>
<td>0.25 to 0.34 mg/L (natural) 0.58 to 0.73 mg/L (natural) 1.00 to 1.06 mg/L (natural) 1.45 to 2.19 mg/L (natural) 2.62 to 3.56 mg/L (natural) 4.32 to 7.97 mg/L (natural)</td>
<td></td>
</tr>
<tr>
<td>Ecologic</td>
<td>Mexico</td>
<td>Children (ages 6-12 years) and adults (ages 13-60 years)</td>
<td>ND to 1.5 mg/L (natural) 1.51 to 4.99 mg/L (natural) 5.0 to 8.49 mg/L (natural) 8.5 to 11.9 mg/L (natural) &gt;12 mg/L (natural)</td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>USA</td>
<td>Women participating in the Nurses’ Health Study (ages 30-55; n [hip fracture] = 53; n [forearm fracture] = 188; n [controls] = 241)</td>
<td>Concentrations in toenails &lt;2.00 ppm 2.00 to 3.35 ppm 3.36 to 5.50 ppm &gt;5.50 ppm</td>
<td></td>
</tr>
</tbody>
</table>
### MUSCULOSKELETAL EFFECTS

<table>
<thead>
<tr>
<th>Study Design</th>
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<th>Exposure</th>
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<tbody>
<tr>
<td>Ecologic</td>
<td>Italy</td>
<td>Residents of two counties</td>
<td>1.45 mg/L (natural), 0.05 mg/L (natural)</td>
<td>Significantly greater rate of fracture incidence, particularly femur fractures (RR for males 4.28 and for females 2.64), in the low-exposure community.</td>
<td>Fabiani et al. 1999</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>Finland</td>
<td>Residents of a rural location (n = 144,627)</td>
<td>≤0.1 mg/L, 0.11 to 0.30 mg/L (natural), 0.31 to 0.50 mg/L (natural), 0.51 to 1.00 mg/L (natural), 1.10 to 1.50 mg/L (natural), &gt;1.50 mg/L (natural)</td>
<td>Age- and area-adjusted RRs for men were 1.0, 1.05 (95% CI 0.90 to 1.22), 0.72 (95% CI 0.51 to 1.02), 1.03 (95% CI 0.81 to 1.32), 0.67 (95% CI 0.46 to 0.97), and 0.98 (95% CI 0.61 to 1.60). Corresponding values for women were 1.0, 0.93 (95% CI 0.84 to 1.02), 1.12 (95% CI 0.93 to 1.34), 1.12 (95% CI 0.96 to 1.31), 1.08 (95% CI 0.88 to 1.32), and 1.08 (95% CI 0.80 to 1.46). Among women aged 50 to 64 years, fluoride was associated with increased risk of hip fracture. Age- and area-adjusted rate ratio for this age group was 2.09 (95% CI 1.16 to 3.76) in the highest-exposure group (&gt;1.5 mg/L) compared with the lowest-exposure group (≤0.1 mg/L).</td>
<td>Kurttio et al. 1999</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Finland</td>
<td>Patients with hip fracture (ages ≥50)</td>
<td>&lt;0.3 mg/L (natural), 1.0 to 1.2 mg/L (artificial)</td>
<td>No difference in incidence of hip fracture among exposure groups. Osteofluorosis was found in 22% of the high exposure group. Fluoride content of the bone was correlated with volumetric density of trabecular bone and osteoid-covered trabecular bone surface.</td>
<td>Arnala et al. 1986</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>Finland</td>
<td>Premenopausal women in a province (ages 47 to 56; n = 3,222)</td>
<td>&lt;0.3 mg/L (natural), 1 to 1.2 mg/L (artificial)</td>
<td>No significant difference in fracture incidence among the fluoridated (15.4%) and nonfluoridated group (13.4%) (P = 0.220).</td>
<td>Kroger et al. 1994</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Finland</td>
<td>Residents in two towns (n = 71,811 and n = 61,587)</td>
<td>&lt;0.1 mg/L, 1 mg/L</td>
<td>In the &lt;0.1-mg/L exposure group, RR was 2.5 (95% CI 1.6 to 3.9) for men and 1.5 (95% CI 1.2 to 1.8) for women. In the group exposed to 1 mg/L, RR was 1.0 for men and women.</td>
<td>Simonen and Laitinen 1985</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>China</td>
<td>Residents of rural communities exposed to various concentrations of fluoride in drinking water (ages ≥50; n = 8,266)</td>
<td>0.25 to 0.34 mg/L (natural), 0.58 to 0.73 mg/L (natural), 1.00 to 1.06 mg/L (natural), 1.45 to 2.19 mg/L (natural), 2.62 to 3.56 mg/L (natural), 4.32 to 7.97 mg/L (natural)</td>
<td>Lowest prevalence of overall bone fracture was found in the 1.00 to 1.06 mg/L group and was significantly lower (P &lt; 0.05) than that of the groups exposed to concentrations ≥4.32 and ≤0.34 mg/L. Prevalence of hip fracture was greatest in the in the 4.32 to 7.97 mg/L group and was significantly higher than the 1.0- to 1.06-mg/L group.</td>
<td>Li et al. 2001</td>
</tr>
<tr>
<td>Ecologic</td>
<td>Mexico</td>
<td>Children (ages 6-12 years) and adults (ages 13-60 years)</td>
<td>ND to 1.5 mg/L (natural), 1.51 to 4.99 mg/L (natural), 5.0 to 8.49 mg/L (natural), 8.5 to 11.9 mg/L (natural), &gt;12 mg/L (natural)</td>
<td>Increased bone fracture (bone types not specified) incidence was observed at concentrations ranging from 1.5 to 4.99 mg/L. A plot of the incidence of fractures in adults versus the average corresponding fluoride concentration by zone indicated a third-order polynomial correlation (R² = 0.9995). Incidence in children was similar, except in one zone. Linear correlation between Dean index for dental fluorosis and the frequency of bone fracture in children (R² = 0.94) and adults (R² = 0.98). Women with higher concentrations of toenail fluoride appeared to be at greater risk of forearm fracture but to have a lesser risk of hip fracture than women with toenail concentrations &lt;2 ppm. Odds ratio of hip fracture in women with &gt;5.50 ppm compared with those with &lt;2.00 ppm was 0.8 (95% CI 0.2 to 4.0). Corresponding adjusted odds ratio for forearm fracture was 1.6 (95% CI 0.8 to 3.1).</td>
<td>Alarcón-Herrera et al. 2001, Feskanich et al. 1998</td>
</tr>
</tbody>
</table>

TABLE 5-1 Continued
cifically address the committee’s charge, this meta-analysis and most of the studies on which it was based were not critically evaluated. The committee restricted its attention to the observational studies that most directly address the study charge: studies that examined long-term exposure to fluoride in the range of 2 to 4 mg/L or above in drinking water. Randomized clinical trials that exposed subjects to higher doses over shorter periods of time were also considered.

The committee considered a number of factors as it evaluated the available data, including the following:

- The committee assumed that fluoride concentrations in bone are the most appropriate measure of exposure. Although difficult to measure in epidemiology studies, bone fluoride concentrations are positively associated with the amount of fluoride exposure, length of exposure, age, and certain diseases such as chronic renal insufficiency (see Chapter 3 for discussion of pharmacokinetic factors that affect fluoride uptake by bone). Use of other fluoride exposure measures is likely to cause measurement error. While exposure measurement error often biases results toward the null, there are many exceptions.

- U.S. exposure estimates presented in Chapter 2 indicate that water will be the major route of exposure for Americans drinking or cooking with water containing fluoride at 4 mg/L but that other sources become more important at concentrations closer to 1 mg/L.

- The incidence of fractures increases dramatically in old age. Minor or moderate traumas cause more fractures in the elderly than in healthy young adults. Other known or suspected risk factors include being female, being postmenopausal, diet (e.g., low calcium), physical inactivity, low body mass index, and use of certain drugs (e.g., corticosteroids) (Ross 1996; Woolf and Åkesson 2003). As a result, age is a very important covariate both as a potential confounder and as an effect modifier; control for age may need to be fairly detailed above age 50.

- Self-reports of fractures are reasonably accurate, although vertebral fractures are typically underreported. Elderly women may overreport total fractures, but the percent of false positives may be lower for fractures of the wrist and hip (Nevitt et al. 1992; Honkanen et al. 1999). Thus, although epidemiological studies would be better if they confirm the presence or absence of fractures, self-reports may be adequate. For example, relative risk measures (risk and rate ratios, but not odds ratios) are unbiased if the outcome is nondifferentially underreported but false positives are negligible (Poole 1985). We might expect the degree of false-positive reporting and underreporting not to differ by fluoride water concentrations, thus tending to attenuate associations.

- Fluoride may have different effects on fractures of different bones (as
suggested by Riggs et al. 1990). Consequently, epidemiologists need to be careful about the degree of aggregation of outcomes. If some bone sites are included that are not susceptible, then relative risk estimates will be biased toward the null; risk or rate differences would not.

- Studies that measure outcome and covariates individually but exposure by group (e.g., by water concentration) use a partially ecologic or group-level design. This design greatly improves the ability to measure and control for covariates relative to pure ecologic studies; control of covariates is one of the major problems in purely ecologic studies. See Appendix C for a description of these design differences.

Below is a review of the available epidemiologic data for evaluating the adequacy of EPA's maximum-contaminant-level goal (MCLG) for fluoride of 4 mg/L and secondary maximum contaminant level (SMCL) of 2 mg/L for protecting the public from bone fractures.

*Studies Relevant to Assessing Risks at 4 mg/L*

**Observational Studies.** The committee is aware of five published observational studies of fractures in subjects exposed to drinking water containing fluoride at 4 mg/L or higher (Sowers et al. 1986, 1991, 2005; Alarcón-Herrera et al. 2001; Li et al. 2001) and another (Kurttio et al. 1999) involving somewhat lower exposures that has some relevance. The first two Sowers papers examine the same cohort, one retrospectively (Sowers et al. 1986) and one prospectively (Sowers et al. 1991). Because the analysis in the 1986 paper is less detailed for fractures (particularly the discussion of potential confounders), it has been given less attention. Features of the key papers are highlighted in Table 5-2.

Sowers et al. (1991) directly assessed the risk of fracture from fluoride at 4 mg/L, reporting adjusted odds ratios (ORs) of 2.1 (95% CI = 1.0 to 4.4) for any fracture, and 2.2 (95% CI = 1.0 to 4.7) for fracture of the hip/wrist/spine in women 55 to 80 years of age at baseline (ORs were also elevated in younger women). The reference group was exposed to fluoride at 1 mg/L. This is a strong study, particularly because of its prospective cohort design. Although the 1993 National Research Council (NRC) report labeled it as ecologic, it is actually an individual-level study with an ecologic exposure measure (such designs are also called semi-individual; see Appendix C). Outcome and important covariates, including age, are measured at the individual level (control of covariates is particularly problematic in fully ecologic studies). This study has some weaknesses: confounding was assessed by using stepwise logistic regression (a common but less than optimal method for assessing confounding) and fractures were self-reported. Self-reports of fractures are often quite reliable (except for the spine, where
TABLE 5-2 Observational Studies of Bone Fractures in Populations Exposed to Fluoride Near 4 mg/L in Drinking Water

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<tbody>
<tr>
<td>Location</td>
<td>Retrospective cohort with ecologic exposure measure</td>
<td>Prospective cohort with ecologic exposure measure</td>
<td>Ecologic</td>
</tr>
<tr>
<td>Location</td>
<td>China, 6 areas with fluoride ranging from 0.25 to 7.97 mg/L</td>
<td>3 areas in Iowa (USA) with fluoride at 1 or 4 mg/L</td>
<td>Guadalupe Valley, Mexico, with fluoride ranging from &lt;1.5 to 16 mg/L</td>
</tr>
<tr>
<td>No. subjects</td>
<td>8,262</td>
<td>827 at baseline, good follow-up</td>
<td>1,437 (333 less than 13 years old)</td>
</tr>
<tr>
<td>Exposure assessment</td>
<td>Ecologic; negligible sources other than water; very-long-term residents; very strong for this type of study</td>
<td>Ecologic; other sources likely in low-exposure groups; long residence time</td>
<td>Ecologic; inconsistent documentation (e.g., use of bottled water mentioned for only one area); permanent residents not defined</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Self-reported fractures validated via x-ray, but lack of fracture not confirmed; recall bias seems unlikely; report all fractures since age 20 or 50, also hip since age 20; count number of subjects with fractures</td>
<td>Self-reported fractures (spine fractures likely underreported) for 5 year follow-up; report all fractures, plus fractures of hip/wrist/spine; count number of subjects with fractures</td>
<td>Self-reported fracture; any fracture “ever occurred without apparent cause, where a bone fracture would not normally be expected to occur”—highly subjective; counts multiple fractures per person</td>
</tr>
<tr>
<td>Confounding</td>
<td>Very similar communities; many individual-level risk factors; imperfect method for covariate control (relying on significance tests)</td>
<td>Similar communities; many individual-level risk factors; imperfect method for covariate control (relying on significance tests)</td>
<td>No variables analyzed other than crude stratification by age (&lt;13, ≥13); major weakness</td>
</tr>
<tr>
<td>Results</td>
<td>U-shaped results for all fractures, increasing trend for hip (age &gt; 20); adjusted ORs (P values) versus 1 mg/L: Fluoride, mg/L</td>
<td>Increased risk at 4 mg/L versus 1 mg/L</td>
<td>Effect measures not presented; percent of fractures increases in adults from 3.1% (&lt;1.5 mg/L) to 7.9% (1.51 to 4.99 mg/L), 8.9% (5 to 8.99 mg/L), but then decreases. P values for the two intermediate levels were 0.046 and 0.041.</td>
</tr>
</tbody>
</table>

Fluoride, mg/L | All sites | Hip |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.62 to 3.56</td>
<td>1.18 (0.35)</td>
<td>1.73 (0.34)</td>
</tr>
<tr>
<td>4.32 to 7.97</td>
<td>1.47 (0.02)</td>
<td>3.26 (0.02)</td>
</tr>
</tbody>
</table>

Total fractures since age 50 also provided.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Location</th>
<th>No. subjects</th>
<th>Exposure assessment</th>
<th>Outcomes</th>
<th>Confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2001)</td>
<td>Strong study</td>
<td>Strong study</td>
<td>Weak study</td>
<td>Additional comments</td>
<td>Suggestive analysis of fracture versus dental fluorosis but insufficient detail</td>
<td></td>
</tr>
<tr>
<td>Sowers et al. (1991)</td>
<td>Strong study</td>
<td>Strong study</td>
<td>Weak study</td>
<td>Additional comments</td>
<td>Suggestive analysis of fracture versus dental fluorosis but insufficient detail</td>
<td></td>
</tr>
<tr>
<td>Alarcón-Herrera et al. (2001)</td>
<td>Strong study</td>
<td>Strong study</td>
<td>Weak study</td>
<td>Additional comments</td>
<td>Suggestive analysis of fracture versus dental fluorosis but insufficient detail</td>
<td></td>
</tr>
<tr>
<td>Kurttio et al. 1999</td>
<td>Historical cohort</td>
<td>Finland, rural communities nationwide</td>
<td>144,000+</td>
<td>Groundwater measurements of almost 9,000 wells</td>
<td>First recorded hip fracture</td>
<td>Analyzed controlling for age and geographic sector. Age adjustment was conducted within broad strata of 50 to 64 and 65 to 80. No information on nutrition, alcohol use, or physical activity.</td>
</tr>
<tr>
<td>Sowers et al. 2005</td>
<td>Prospective cohort with both ecologic and individual-level exposure measures</td>
<td>Same three areas of Iowa as earlier study</td>
<td>1,300 women aged 20 to 92 (average, 55)</td>
<td>Ecologic (area of study)</td>
<td>Individual (serum fluoride concentration)</td>
<td>Self-reported fracture, confirmed by medical records or x-ray copies, if available. Lack of fractures apparently not confirmed. Fractures separated into likely osteoporotic (hip, spine, wrist, ribs) and other.</td>
</tr>
<tr>
<td>Sowers et al. 2005</td>
<td>Prospective cohort with both ecologic and individual-level exposure measures</td>
<td>Same three areas of Iowa as earlier study</td>
<td>1,300 women aged 20 to 92 (average, 55)</td>
<td>Ecologic (area of study)</td>
<td>Individual (serum fluoride concentration)</td>
<td>Self-reported fracture, confirmed by medical records or x-ray copies, if available. Lack of fractures apparently not confirmed. Fractures separated into likely osteoporotic (hip, spine, wrist, ribs) and other.</td>
</tr>
</tbody>
</table>

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TABLE 5–2 Continued

<table>
<thead>
<tr>
<th>Kurtio et al. 1999</th>
<th>Sowers et al. 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
<td>Ecologic: 2.55-fold increased risk ($P = 0.07$) osteoporotic fracture at 4 mg/L versus 1 mg/L for all women (age breakdown not provided) after adjustment (including bone mineral density of femoral neck). Individual: RR = 1.16 ($P = 0.66$) for osteoporotic fracture versus log of serum fluoride for all women, after adjustment (including bone mineral density of femoral neck).</td>
</tr>
<tr>
<td>For comparisons between the &gt;1.5 mg/L group and the &lt;0.1 mg/L group (ages 50 to 65), adjusted RR = 2.09 (95% CI, 1.16 to 3.76) in women, RR = 0.87 (95% CI, 0.35 to 2.16) in men. For all ages combined, no associations apparent. For fluoride as a continuous variable, RR = 1.44 (95% CI, 1.12 to 1.86) for women below age 65 at start of follow-up, and RR = 0.75 (95% CI, 0.51 to 1.12) for men in same age stratum (age and region adjusted). Women ages 55 to 69 had the most elevated RR in the continuous-variable analysis. Among separate 5-year components of follow-up period, the results were inconsistent.</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>Strong study</td>
</tr>
<tr>
<td>Suggestive of hip fracture risk, with continuous gradient from lowest to highest exposures</td>
<td>Weak association between bone density and serum fluoride (e.g., adjusted $\beta = 0.011 \pm 0.0073$ (SE), $P = 0.13$ for femoral neck). Use of serum fluoride concentration may bias results toward null if there is nondifferential error relative to bone fluoride concentrations. Bone mineral density may be, in part, an intermediate variable.</td>
</tr>
</tbody>
</table>

**TABLE 5–2 Continued**

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underreporting is typical). Details about the interviewers (training or blinding to exposure) were not provided. The paper also examined fractures in a community with high calcium concentrations in water: the adjusted OR for fracture of the hip/wrist/spine was 1.6 (95% CI = 0.71 to 3.4) for the older women and 0.30 (95% CI = 0.04 to 3.4) for younger women (the ORs for all fractures were similar). The regression analysis comparing the high fluoride and the reference communities was adjusted for calcium intake, but it produced no change.

The newest study by Sowers et al. (2005) investigated bone fracture in relation to fluoride concentration in drinking water. The authors measured serum fluoride, providing a potentially improved exposure assessment. In this cohort study, fractures were assessed prospectively for 4 years. Fractures were self-reported and then confirmed with medical records or x-ray copies, if available; lack of fractures was apparently not confirmed. Sowers et al. (2005) collected individual-based information on people from the same regions as the 1986 and 1991 studies. They collected serum fluoride concentrations and bone mineral density of the hip, radius, and spine. The number of subjects was considerably expanded (n = 1,300) from the earlier studies. Although there may be overlap in specific subjects, all the fracture events were recent. The authors reported risk ratios of fractures in the high fluoride area that were similar to those in the previous studies (risk ratio = 2.55, P = 0.07, even when adjusting for bone mineral density, which could function as an intervening variable between water ingestion and fracture outcome). Use of ecologic exposure measures need not cause bias due to exposure measurement error (see Appendix C).

Serum fluoride concentration was higher in the community with fluoride at 4 mg/L in drinking water. Bone and serum concentrations are related but the latter have more noise—potentially much more, depending on how samples were collected. Serum fluoride concentrations can vary within individuals, returning to baseline within hours of exposure.

Fasting serum fluoride concentrations are considered a good (although not necessarily perfect) measure of long-term exposure and of bone fluoride concentrations (Ericsson et al. 1973; Parkins et al. 1974; Taves and Guy 1979; Waterhouse et al. 1980; Whitford 1994; Clarkson et al. 2000; see also Chapter 2 for a discussion of biomarkers and Chapter 3 on pharmacokinetics). Although methods for serum collection are not described in the paper, Sowers stated that fasting serum concentrations were taken “whenever possible” (M.F. Sowers, University of Michigan, personal commun., July 1, 2005). Measured serum fluoride concentration was not statistically associated with fracture incidence in the adjusted model, including bone density, a potential intermediate variable (measured serum fluoride was only weakly associated with bone mineral density). However, it is unclear whether serum fluoride was a useful surrogate for concentrations in bone.
or chronic exposure here; random error would tend to bias results toward the null. Table 2 in the Sowers et al. (2005) paper indicated that long-term residency in the high-fluoride region was not associated with appreciably higher serum fluoride than short-term residency.

Besides differences in osteoporotic, but not other, fracture rates, these populations differed markedly with respect to smoking rates and hormone replacement (both lowest in the reference group) and physical activity (lowest in the high-fluoride group). It is unclear whether these factors were examined as potential confounders for fractures. Age subgroups were not presented in the new Sowers et al. study, so differences within age groups cannot be assessed and comparisons with the other observational studies on fractures cannot be made.

For all the Sowers studies, there is an unresolved question about whether the referent group (area with low fluoride and low calcium) might have a low fracture rate because of risk factors that are not controlled for in the studies, particularly as the high-calcium/low-fluoride region also showed increased fracture rates compared with the referent region. Potential bias due to such differences might be exacerbated by the use of an ecologic exposure measure (see Appendix C).

The study by Li et al. (2001) complements the Sowers studies in several ways, having a larger size and relatively strong exposure assessment for a partially ecologic study. It has a retrospective cohort design, increasing the potential for outcome and exposure misclassification, but these problems were addressed by the authors. Although exposure was assessed on the group level, exposure was finely categorized and other sources of fluoride exposure were estimated to be negligible. (Nonwater exposures to fluoride were presumably more important in the Sowers studies.) Communities were quite similar and individual-level risk factors were assessed. Fractures were self-reported; confirmation with x-rays showed very high validity (526 fractures confirmed among the 531 subjects reporting fractures). This study also has weaknesses. Confounding was assessed by statistical testing; the authors included a covariate in the logistic regression if they first found a statistically significant ($P < 0.05$) relationship between the variable and outcome analyzed bivariately. (Confounding should be judged by examining the effect measure, not statistical testing; see Rothman and Greenland 1998.) Absence of fractures was not confirmed, potentially biasing outcomes if false-positive reporting of fractures is expected to be more than an isolated occurrence. However, a limited number of sensitivity analyses of confounding performed by the committee did not explain the effect; recall bias seems an unlikely explanation for the U-shaped exposure-response curve (for all fractures since age 20), with the minimum fractures in the reference group of 1 mg/L. The dose-response curve for all fractures is plausible: some, but not all, animal studies suggest a biphasic relationship between bone fluoride
concentrations and bone strength (see discussion earlier in this section on cellular and molecular aspects).

The Li et al. study did not directly assess fluoride at 4 mg/L. However the exposure group just above 4 mg/L (4.32 to 7.97 mg/L) showed an increase in all fractures since age 20 (OR = 1.47, P = 0.01, estimated 95% CI = 1.10 to 1.97), all fractures since age 50 (OR = 1.59, P = 0.02, estimated 95% CI = 1.08 to 2.35), and hip fractures since age 20 (OR = 3.26, P = 0.02, estimated 95% CI = 1.21 to 9.81). The exposure group just below 4 mg/L (2.62 to 3.56 mg/L) showed the following: all fractures since age 20 (OR = 1.18, P = 0.35, estimated 95% CI = 0.83 to 1.67), all fractures since age 50 (OR = 1.04, P = 0.87, estimated 95% CI = 0.65 to 1.66), and hip fractures since age 20 (OR = 1.73, P = 0.34, estimated 95% CI = 0.56 to 5.33). CI values were estimated by the committee using the approach of Greenland (1998). Although the latter results are not statistically significant at the 0.05 level, they are consistent with an upward trend (increasing dose-response relationship), particularly the result for hip fracture. The inclusion of all fractures is likely to bias ORs toward the null.

Although the authors did not estimate trend, Figures 2 and 3 presented in the paper by Li et al. (2001) suggest that linear trends in proportions from the 1.00 to 1.06 mg/L category up would provide a reasonable fit in that range. Using a generalized linear model with the binomial distribution and the identity link, and midranges for the exposure categories, the committee estimated absolute increases in fractures of 1.3% (95% CI = 0.3 to 2.2, P = 0.01) for the increment from 1.00 to 4.00 mg/L for overall fractures since age 20, 0.4% (95% CI = 0.0 to 0.8, P = 0.04) for hip fractures since age 20, and 0.9% (95% CI = 0.2 to 1.7, P = 0.02) for overall fractures since age 50.

The U-shaped exposure-response curve for all fractures combined (but not hip fractures) for this population of individuals provides an interesting and potentially important finding. Whereas the trend for fractures appears to increase from 1.00 to 4.00 mg/L, it must be appreciated that the fracture rate in the 1.00 to 1.06 mg/L category was lower than the rate in the category with the lowest intake.

Estimated fluoride exposure in the Li study is higher than for the Sowers studies (see Table 5-4 later in this chapter). Assuming that exposure was predominantly due to water, the committee estimated that participants in the Li study consumed on average about 2.5 L per day for the 2.62- to 3.56-mg/L group and 2.3 L per day for 4.32- to 7.97-mg/L group (versus 0.9 to 1.2 L per day for the Sowers studies). These water consumption levels are in the 90th to 95th percentile for the United States (see Appendix B).

Alarcón-Herrera et al. (2001) is a much weaker ecologic study with little attention to covariates other than a rough stratification by age (see
In addition, a retrospective cohort study in Finland by Kurttio et al. (1999) is pertinent to the issue of fracture risk at 4 mg/L, even though relatively few wells in that study had drinking water with fluoride concentrations that high. Residents were grouped into exposure categories based on modeled fluoride concentrations in well water closest to their residence: \leq 0.1, 0.11 to 0.30, 0.31 to 0.50, 0.51 to 1.00, 1.10 to 1.50, and >1.5 mg/L (ranging up to 2.4 mg/L). Fluoride monitoring results among water samples for the highest modeled group varied from below detection to about 6 mg/L. Hospital discharge registers were tracked between 1981 and 1994 for reports of hip fracture among the cohort. For all ages combined, no associations were found between fluoride content in drinking water and hip fracture. However, analysis of age strata (50 to 64 and 65 to 80) indicated an increased risk of hip fracture in women aged 50 to 64 exposed to fluoride at >1.5 mg/L (adjusted rate ratio of 2.09%; 95% CI, 1.16 to 3.76; based on 13 cases [3,908 person years] compared with those in the least exposed group (\leq 0.1 mg/L). Some covariates were adjusted by using ecologic measures, an imperfect technique.

Clinical Trials of Osteoporosis Treatment. Using the Cochrane Handbook methodology, Haguenauer et al. (2000) performed a meta-analysis of randomized clinical trials of fluoride in postmenopausal women with primary osteoporosis. Eleven studies met the inclusion criteria; analyses of specific end points included only a subset. The summary relative risk estimate for new vertebral fractures was slightly decreased: 0.87 (95% CI = 0.51 to 1.46) for 2 years of treatment (four trials) and 0.90 (95% CI = 0.71 to 1.14) for 4 years (five trials). The summary relative risk estimate for new nonvertebral fractures was increased: 1.20 (95% CI = 0.68 to 2.10) after 2 years (one trial) and 1.85 (95% CI = 1.36 to 2.50) after 4 years (four trials); the latter association was strongest in trials using high-dose, non-slow-release forms of fluoride. See Table 5-3 for the four studies included in the analysis of nonvertebral fractures after 4 years. All four studies were prospective, double-blinded, and placebo-controlled; all subjects received supplemental calcium. There was loss to follow-up, particularly in the study of Kleerekoper et al. (1991), but it was similar in frequency in treated and placebo groups.

Table 5-3 reports relative risks of nonvertebral fractures at 4 years. Rate ratios are also provided for several studies. Hip fracture results are reported only for Riggs et al. (1990); the number of hip fractures in the other trials was at most one per group. Riggs et al. reported both complete fractures and total fractures. Total fractures equal complete plus incomplete “stress” fractures; the latter were observed by roentgenography in participants re-
TABLE 5-3 Four Randomized Clinical Trials Examining Nonvertebral Fractures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Enrollment: Exposed and Placebo</th>
<th>Participation&lt;sup&gt;a&lt;/sup&gt; Exposed and Placebo</th>
<th>Relative Risk (95% CI) Nonvertebral Fractures&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Rate Ratio (95% CI) Nonvertebral Fracture&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reginster et al. 1998</td>
<td>Fluoride at 20 mg/day as sodium monofluorophosphate, 4 years</td>
<td>100, 100</td>
<td>84%, 81%</td>
<td>1.1 (0.5, 2.4)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pak et al. 1995</td>
<td>NaF at 50 mg/day slow-release, 4 cycles: 12 months on, 2 months off</td>
<td>54, 56</td>
<td>77%, 72%</td>
<td>0.6 (0.2, 2.5)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kleerekoper et al. 1991</td>
<td>NaF at 75 mg/day, 4 years</td>
<td>46, 38</td>
<td>60%, 61%</td>
<td>1.5 (0.7, 3.5)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Riggs et al. 1990</td>
<td>NaF at 75 mg/day, 4 years</td>
<td>101, 101</td>
<td>77%, 80%</td>
<td>1.6 (1.0, 2.5) complete 2.5 (1.7, 3.7) total&lt;sup&gt;d&lt;/sup&gt; 2.3 (0.6, 8.8) complete, hip</td>
</tr>
</tbody>
</table>

<sup>a</sup>Participating person-time divided by total possible person-time.
<sup>b</sup>Risks were computed by dividing the number of first incident fractures (at most one per subject) by the number of enrolled subjects.
<sup>c</sup>Rates were computed by dividing the number of incident fractures (possibly more than one per subject) by participating person-time.
<sup>d</sup>The numbers that appear to have been used in the meta-analysis of Haguenauer et al. (2000); see their Figure 5.
<sup>e</sup>Areas of increased isotope uptake detected via radionuclide bone scan.
<sup>f</sup>In this study, total fractures = complete + incomplete “stress” fractures, the latter observed by roentgenography in participants reporting acute lower extremity pain syndrome.

Comparison of Exposure in Randomized Clinical Trials and Observational Studies. Despite the methodological strengths of the randomized clinical trials, their use in this review has limitations. In particular, fluoride exposures in the trials were higher in magnitude (20 to 34 mg/day) than
in observational studies (5 to 10 mg/day for 4 mg/L) but shorter in time (years versus decades). One possibility is to compare studies using total fluoride exposure in absolute mass units. Because some biological effects (e.g., stimulation of osteoblasts) may occur only at high doses, results from clinical trials may not be directly comparable to risks due to long-term exposure to fluoride in water. On the other hand, the committee assumes that bone fluoride concentration is the most appropriate measure of exposure for examining fracture risk. Data permitting, it could be possible to compare the bone fluoride concentrations reached in the randomized clinical trials with those in the observational studies.

Of the four randomized clinical trials in the fracture meta-analysis, the committee was able to locate bone fluoride measurements for only one. Of the 202 postmenopausal women in the Riggs study, bone fluoride was measured before treatment and at 4 years in 43 treated and 35 placebo subjects (Lundy et al. 1995). Unfortunately, the data are presented only in a figure and in units of μmol of fluoride per mmol of calcium. The latter, however, can be approximately converted to mg/kg ash by using the following factors: 1 g of calcium per 7 g wet weight of bone (Mernagh et al. 1977) and 0.56 g of ash per g wet weight of bone (Rao et al. 1995). Using this conversion, the before-treatment bone ash fluoride concentrations were about 1,700 mg/kg in both the treated and the placebo groups. Taking the imprecision of the conversion factors into account, this value is consistent with reported concentrations for healthy, untreated persons living in areas without particularly high water fluoride concentrations and no other exceptional sources of fluoride intake (see Chapter 3). Four years later, bone ash concentrations were slightly higher in the placebo group and about 12,000 mg/kg in the treated group. The latter value should overestimate concentrations in the exposed group of the trial, because the average exposed subject in the Riggs study participated 3.1 years (Table 5-3).

Ideally, one would estimate bone concentrations in the other trials by using a pharmacokinetic model. Because the committee did not have an operational pharmacokinetic model, a regression model was used to estimate bone concentrations based on total fluoride exposure during clinical trials (see Chapter 3). Total exposures (Table 5-4) were estimated with the nominal daily dose and the average length of participation of the exposed group. The bone concentration for Riggs et al. estimated by this technique (7,400 mg/kg) is less than the value measured by Lundy et al. (roughly 12,000 mg/kg), but the latter examined a subset of subjects who had completed the full 4 years of the study. The regression model estimates 9,100 mg/kg in subjects completing 4 years. Although that estimate is still less than the measured concentration, Chapter 3 noted that the regression model may underestimate bone concentrations in fluoridated areas. Of the four clinical trials in Table 5-4, three were American. Fluoride exposure and concentra-
tions in bone may be overestimated for the Pak study because of the use of a slow-release, less bioavailable form of fluoride. In sum, average fluoride bone concentrations among treated trial participants appear to range from about 5,400 to 12,000 mg/kg.

Comparison of Results of Randomized Clinical Trials and Observational Studies. Table 5-4 also includes estimates of total exposure and average bone fluoride for two observational studies. The committee estimated average fluoride concentrations in bone in the study by Sowers et al. (1991) using the regression model developed for chronic water exposure in Chapter 3. This model predicts bone concentrations based on concentration of fluoride in water, length of exposure, and sex. The result is in the same range as the clinical trials. Since the regression model does not take water consumption rates into account, it should underpredict bone fluoride concentrations for people with high water consumption. The bone fluoride estimates for Li et al. (2001) are, therefore, probably underestimates. Estimates of bone fluoride concentrations could be improved through the use of pharmacokinetic models (see Chapter 3).

Table 5-4 summarizes fracture outcomes for the four clinical trials (nonvertebral) and observational studies. There are a number of differences in the way the outcome data were collected and analyzed. For example, Li et al. counted fractures occurring since age 20 (or age 50, not shown), a longer observation period than the other studies; Li et al. and Sowers et al. measured fractures in different bones than those studied in the clinical trials; if trials use subjects from fluoridated areas, the subjects receiving placebos are from areas with fluoride close to 1 mg/L. Although the comparison involves several assumptions and uncertainties, the estimated concentrations of fluoride in bone and results of the randomized clinical trials generally appear consistent with those of the observational studies.

Interpretation of Weight of Evidence of the Fracture Data on Fluoride at 4 mg/L. For making causal inferences, many epidemiologists prefer to formulate and test specific competing hypotheses (e.g., Rothman and Greenland 1998). Other epidemiologists find it useful to weigh the evidence in light of some traditional “criteria” (more properly, guidelines) for examining whether observed associations are likely to be causal (Hill 1965). The discussion below provides a perspective on how the committee evaluated and viewed the strength of the collective evidence on possible causal associations.

- Consistency: Despite some design or data weaknesses, there is consistency among the results of all the observational studies using ecologic exposure measures. That is, none of the studies that included population ex-
### TABLE 5-4 Estimated Bone Fluoride Concentrations and Bone Fracture Risks in Randomized Clinical Trials and Observational Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fluoride Exposure (mg/day)</th>
<th>Average Length Exposure (years)</th>
<th>Estimated Total Exposure (g)</th>
<th>Estimated Bone Fluoride (mg/kg ash)</th>
<th>Relative Risks (RR) or Odds Ratios (OR) and (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized clinical trials</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Reginster et al. 1998 (Belgium)</td>
<td>20</td>
<td>3.4</td>
<td>24</td>
<td>5,400&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.1 (0.5, 2.4) RR nonvertebral, 4 years</td>
</tr>
<tr>
<td>Pak et al. 1995 (USA)</td>
<td>23 (slow-release)</td>
<td>3.1</td>
<td>25</td>
<td>5,500&lt;sup&gt;b-c&lt;/sup&gt;</td>
<td>0.6 (0.2, 2.5) RR nonvertebral, 4.7 years</td>
</tr>
<tr>
<td>Kleerekoper et al. 1991 (USA)</td>
<td>34</td>
<td>2.4</td>
<td>30</td>
<td>6,200&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5 (0.7, 3.5) RR nonvertebral, 4 years</td>
</tr>
<tr>
<td>Riggs et al. 1990 (USA)</td>
<td>34</td>
<td>3.1</td>
<td>38</td>
<td>7,400&lt;sup&gt;b&lt;/sup&gt; (12,000)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.6 (1.0, 2.5) RR complete nonvertebral, 4 years 2.5 (1.7, 3.7) RR total nonvertebral, 4 years 2.3 (0.6, 8.8) RR complete hip, 4 years</td>
</tr>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sowers et al. 1991 Baseline age 55 to 80 (4 mg/L area)</td>
<td>4.88&lt;sup&gt;e&lt;/sup&gt;</td>
<td>35.9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>64</td>
<td>7,200&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.1 (1.0, 4.4) OR any fracture, 5 years 2.2 (1.0, 4.7) OR hip/wrist/spine, 5 years</td>
</tr>
<tr>
<td>Sowers et al. 2005 Age 20 to 92 (4 mg/L area)</td>
<td>3.66</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.55 (&lt;i&gt;P&lt;/i&gt; = 0.07) OR osteoporotic, ecologic 1.16 (&lt;i&gt;P&lt;/i&gt; = 0.66) OR osteoporotic, log serum concentration</td>
</tr>
<tr>
<td>Li et al. 2001 2.62 to 3.56 mg/L</td>
<td>7.85&lt;sup&gt;i&lt;/sup&gt;</td>
<td>64&lt;sup&gt;j&lt;/sup&gt;</td>
<td>180</td>
<td>&gt;6,200&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.18 (&lt;i&gt;P&lt;/i&gt; = 0.35) OR, any site since age 20 1.73 (&lt;i&gt;P&lt;/i&gt; = 0.34) OR, hip since age 20 1.47 (&lt;i&gt;P&lt;/i&gt; = 0.02) OR, any site since age 20 3.26 (&lt;i&gt;P&lt;/i&gt; = 0.02) OR, hip since age 20</td>
</tr>
<tr>
<td>4.32 to 7.97 mg/L</td>
<td>14.1&lt;sup&gt;i&lt;/sup&gt;</td>
<td>61&lt;sup&gt;j&lt;/sup&gt;</td>
<td>320</td>
<td>&gt;11,000&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>When applied to cohort data, ORs overestimate RRs; the bias is small when odds are small as they are here.
Estimated using regression model for clinical trials (Chapter 3) based on total exposure. Bone concentrations for U.S. studies may be underestimated because of background exposure.

Possibly overestimated because of the use of a less bioavailable form of fluoride.

Approximate bone concentration measured in a subset exposed for 4 years.

Average estimated fluoride intake for ages 55 to 80 in 4-mg/L area from Sowers et al. (1986).

Average residence time from Sowers et al. 1986 (baseline) plus 5 years.

Estimated using regression model for water exposure (Chapter 3). Because of limitations in the regression model, these estimates do not take into account differences in water consumption. This may cause underestimation of bone fluoride concentrations for people with high water consumption rates, as estimated for participants in Li et al. (2001).

Average length of exposure not available. Based on water fluoride concentrations alone, the average estimated bone concentrations are about 6,700 mg/kg ash (Chapter 3).

Estimated exposures for these groups are from Li et al. (2001).

Average exposure length equals average age, based on lifetime exposure.
posures above 4 mg/L found null or negative (inverse) associations between fluoride and bone fractures. There is probably minimal publishing bias here because of the intense interest on both sides of the fluoride controversy. Further, all the studies with exposure categories of approximately 2 mg/L and above in water showed elevated relative risks of fractures for these exposure estimates. However, the one study using an individual exposure measure found no association between fracture risk and serum fluoride. Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to show an association might have been diminished.

- **Strength of association:** Although weak associations (e.g., small relative risks) can be causal, it is harder to rule out undetected biases. As indicated in Table 5-2, relative risk estimates generally varied from about 1.5 to 2.2 for studies with ecologic measures of exposure.

- **Biologic plausibility/coherence:** The weight of evidence of observational studies is increased when qualitative as well as quantitative; biochemical, physiological, and animal data suggest a biologically plausible mechanism by which a potential risk factor such as fluoride could cause adverse effects. In this instance, the type of physiological effect of fluoride on bone “quality” and the fractures observed in animal studies are consistent with the effects found in the observational studies. Furthermore, the results of the randomized clinical trials are consistent with an increased risk of non-vertebral fractures at fluoride concentrations in bone that may be reached by lifetime exposure to water at 4 mg/L.

- **Dose-response (biological gradient):** For the most part, the observational studies discussed above observed higher fracture risk with higher exposure compared with 1 mg/L. The combined findings of Kurttio et al. (1999), Alarcón-Herrera et al. (2001), and Li et al. (2001) lend support to gradients of exposure and fracture risk between 1 and 4 mg/L.

The remaining traditional guidelines of Hill and others are not major issues here: time sequence of effect after exposure is fulfilled in all the observational studies and the clinical trials; none of those designs was cross-sectional and all were able to assess sequence. Specificity of effect or exposure is rarely germane in environmental epidemiology. Experiment (that is, effect of removal of exposure) does not apply in this instance.

When papers using different designs or studying disparate populations are evaluated, findings of consistency among these studies do not require that the doses, exposures, or relative risks be the same. (Such quantitative reconciliation is pertinent for efforts to establish unit risks for quantitative risk assessment, pooling studies, or meta-analyses, and assignment of specific potencies goes far beyond the charge or assessment by the committee.) Further, it is not necessary that there be exact quantitative correspond-
MUSCULOSKELETAL EFFECTS

dence between animal and human data and physiologic, and epidemiologic exposures.

The weight of evidence supports the conclusion that lifetime exposure to fluoride at drinking water concentrations of 4 mg/L and higher is likely to increase fracture rates in the population, compared with exposure to fluoride at 1 mg/L, particularly in some susceptible demographic groups that are prone to accumulating fluoride into their bones.

Studies Relevant to Assessing Risks at 2 mg/L

The committee found four observational studies that involved exposures to fluoride around 2 mg/L (see Table 5-5). By far the strongest of those studies was by Kurttio et al. (1999). As described above, residents were grouped into exposure categories based on modeled fluoride concentrations in well water closest to their residence (≤0.1, 0.11 to 0.30, 0.31 to 0.50, 0.51 to 1.00, 1.10 to 1.50, and >1.5 mg/L [ranged up to 2.4 mg/L]) and hospital discharge registers were tracked for reports of hip fracture. Whereas no associations between fluoride content in drinking water and hip fracture were found for all ages combined, analysis of age strata (50 to 64 and 65 to 80 years) indicated an adjusted rate ratio of 2.09 (95% CI, 1.16 to 3.76) for hip fracture in women aged 50 to 64 exposed to fluoride at >1.5 mg/L.

Another study, performed in Finland, found no evidence of increased risk when hip fracture rates were compared in populations exposed to fluoride at ≤0.3, 1.0 to 1.2, and >1.5 mg/L (Arnala et al. 1986). However, this study had many weaknesses, including incomplete reporting methods, insufficient control of confounding, inability to assess cumulative exposure, and the possibility of nonsystematic or biased case ascertainment. It focused primarily on evaluating fluoride content and the histomorphometry of bone samples taken from the iliac crest of hip fracture patients and had the advantage of providing data on bone fluoride concentrations. Mean fluoride concentrations (± standard deviation) in bone were found to be 450 ± 190 mg/kg, 1,590 ± 690 mg/kg, and 3,720 ± 2,390 mg/kg in the low-, middle-, and high-exposure groups, respectively.

A study in France investigated fracture rates in relation to fluoride-using subjects enrolled in a different study on aging (Jacqmin-Gadda et al. 1995). Two fluoride exposure groups were compared: 0.05 to 0.11 mg/L and 0.11 to 1.83 mg/L. The odds ratio for hip fractures for the higher exposure group was 1.86 (95% CI, 1.02 to 3.36). The odds ratio for any fractures was 0.98 (95% CI, 0.80 to 1.21). These odds ratios were adjusted for age, gender, and Quetelet index for hip fractures and by age and gender for total fractures. (The authors selected confounders to include in their model on the basis of “statistical significance,” although a more appropriate approach would have been to select covariates based on how much they change the odds...
TABLE 5-5  Studies Relevant to Assessing Bone Fracture Risks from Exposure to Fluoride at 2 mg/L in Drinking Water

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Semieologic; individual outcome data and ecologic exposure measure</td>
<td>Nested case control analysis drawn from cross-section study that was the first phase of a prospective cohort study.</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Finland, communities</td>
<td>France</td>
</tr>
<tr>
<td><strong>No. subjects</strong></td>
<td>462 fractures among a population of unspecified size</td>
<td>3,777 subjects age 65 and older from 75 civil parishes (mean residence time 41 years)</td>
</tr>
<tr>
<td><strong>Exposure assessment and categories</strong></td>
<td>Ecologic; exposure assignments drawn from a 1974 report by the National Board on Health on the fluoride content of drinking water in different communities Communities with fluoride at &lt;0.3 mg/L, 1.0 to 1.2 mg/L, and &gt;1.5 mg/L</td>
<td>Two measurements were taken in 1991 and routinely thereafter (frequency not specified). Two exposure categories: 0.05 to 0.11 mg/L and 0.11 to 1.83 mg/L</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Hip fractures among men and women combined, for age 50+. Facts due to severe trauma excluded.</td>
<td>Hip fractures</td>
</tr>
<tr>
<td><strong>Effect measure</strong></td>
<td>Comparison of age-adjusted 10-year incidence of hip fracture for ages 50+ and component age decades. Binomial t test used to compare age-adjusted hip fracture rates.</td>
<td>OR using multiple logistic regressions, controlling for confounders based on interview data.</td>
</tr>
<tr>
<td><strong>Chance</strong></td>
<td>No confidence intervals or $P$ levels were provided.</td>
<td>95% CI and $P$ values given</td>
</tr>
<tr>
<td><strong>Confounding</strong></td>
<td>Age-adjustment only. No information on whether women were postmenopausal. No distinction between rates for males and females.</td>
<td>Age, gender, Quetelet index (kg/height² in m), smoking, and sports activity</td>
</tr>
<tr>
<td>Fabiani et al. (1999)</td>
<td>Kurttio et al. (1999)</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Semiecologenic; individual outcome data and ecologic exposure measures</td>
<td>Historical cohort.</td>
<td></td>
</tr>
<tr>
<td>Two regions of central Italy Avezzano (lower fluoride in water) and Bracciano (higher fluoride in water) 935 in Avezzano 190 in Bracciano; subjects treated in a public hospital from each region Drinking water sampled twice a year (years not specified), and one summary concentration was assigned to each region as a weighted mean. Avezzano (0.05 mg/L; range 0.040 to 0.058 mg/L; population of about 126,000) Bracciano (1.45 mg/L; range 0.15 to 3.40 mg/L; population of about 73,000) Fractures at specific anatomical sites, reported by gender</td>
<td>Finland: rural communities nationwide Groundwater measurements of almost 9,000 wells. Fluoride concentrations estimated for each residence by using weighted medians, smoothed interpolations. Categories: &lt;0.1, 0.1 to 0.3, 0.3 to 0.5, 0.5 to 1.0, 1 to 1.5, and &gt; 1.5 mg/L. Highest category corresponded to sampled concentrations of less than detection level to approximately 6 mg/L.</td>
<td></td>
</tr>
<tr>
<td>Rates and 95% CI based on age-adjusted rates per 1,000 person years.</td>
<td>Crude and adjusted rate ratios using Cox regression based on person years, compared with lowest exposure group. Age stratification based on age at start of follow-up period. Fluoride analyzed as categorical and continuous variable.</td>
<td></td>
</tr>
<tr>
<td>95% CIs</td>
<td>95% CI around the rate ratio.</td>
<td></td>
</tr>
</tbody>
</table>
| Authors relied on similarity of region to control for confounding. Analysis did not stratify or adjust for age, although mean ages of cases are shown (including whether the probabilities of their differences are $P < 0.05$). | Analyzed controlling for age and geographic sector. Age adjustment was conducted within broad strata of 50 to 64 and 65 to 80 years. No information on nutrition, alcohol use, or physical activity.
<table>
<thead>
<tr>
<th>TABLE 5-5 Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>Age-combined totals similar: 12.4/10,000 in low-fluoride, 11.9/10,000 in fluoridated, and 12.4/10,000 in high-fluoride areas. Component age groups generally similar to each other across exposure groups, except that age 80+ had lower incidence in the high-fluoride area.</td>
</tr>
<tr>
<td><strong>Overall value of study regarding evaluation fracture risk at 2 mg/L</strong></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
</tr>
</tbody>
</table>

Results Age-combined totals similar: 12.4/10,000 in low-fluoride, 11.9/10,000 in fluoridated, and 12.4/10,000 in high-fluoride areas. Component age groups generally similar to each other across exposure groups, except that age 80+ had lower incidence in the high-fluoride area.

For higher versus lower fluoride exposures: OR = 1.86 (1.02 to 3.36), \( P = 0.04 \) for hip fractures; OR = 0.98 (0.80 to 1.21) for all fractures. ORs adjusted for variables associated with hip fractures (age, gender, Quetelet) or total fractures (age, gender). Calcium in water did not appear to be included in the model.

Rates for low-fluoride area were statistically greater compared with Bracciano in the following categories: Females: femoral neck (hip), femur NOS (not otherwise specified), proximal humerus, nose, wrist Males: femoral neck (hip), femur NOS, nose, wrist Specifically for hip fracture (Avezanno/Bracciano, rate per 1,000 person-years): males, 0.28/0.06, RR = 4.28 (95% CI, 4.16 to 4.40), average ages 70 and 52, respectively; females, 0.75/0.28, RR = 2.64 (95% CI 2.54 to 2.75), average ages 75 and 78, respectively.

<table>
<thead>
<tr>
<th>Fabiani et al. (1999)</th>
<th>Kurttio et al. (1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Weak

Serious design and analysis limitations. No data that would inform an assessment of a gradient. The dimension of the reported protective effect is not credible.

For comparisons between the >1.5-mg/L group and the <0.1-mg/L group (ages 50 to 65):
Adjusted RR = 2.09 (95 CI, 1.16 to 3.76) in women, RR = 0.87 (95% CI, 0.35 to 2.16) in men.
For all ages combined, no associations apparent.
For fluoride as a continuous variable: RR = 1.44 (95% CI, 1.12 to 1.86) for women below age 65 at start of follow-up, and RR = 0.75 (95% CI, 0.51 to 1.12) for men in same age stratum (age and region adjusted). Women ages 55 to 69 had the most elevated RR in the continuous-variable analysis. Among separate 5-year components of follow-up period, the results were inconsistent.
Suggestive of hip fracture risk, with continuous gradient from lowest to highest exposures.
The committee found that because no data were presented on the distribution of fluoride exposure within the different groups, because data on gender and age were not reported separately, and because no parameters for assessing cumulative exposure were provided, reliable conclusions could not be drawn from this study.

Fabiani et al. (1999) conducted a study in two sociodemographically similar regions in central Italy. One region had fluoride concentrations in drinking water of 0.05 mg/L and the second region had fluoride at 1.45 mg/L. A significantly greater rate of fracture incidence, particularly femur fractures, were found in the low-exposure community. The relative risk was 4.28 (95% CI, 4.16 to 4.40) for males and 2.64 (95% CI, 2.54 to 2.75) for females. These risks were based on age-adjusted rates per 1,000 person-years. However, the number of cases was not provided and the mean age of cases in the two towns varied greatly in some instances. The investigators relied on similarity of regions to control for confounding, but it should be noted that the high-fluoride area included seven towns near Rome, whereas the lower-fluoride area included 35 towns further from Rome. Because of the serious design and analysis limitations of the study, the committee placed little weight on this study.

Overall, the committee finds that the available epidemiologic data for assessing bone fracture risk in relation to fluoride exposure around 2 mg/L is suggestive but inadequate for drawing firm conclusions about the risk or safety of exposures at that concentration. There is only one strong report to inform the evaluation, and, although that study (Kurttio et al. 1999) indicated an increased risk of fractures, it is not sufficient alone to base judgment of fracture risk for people exposed at 2 mg/L. It should be considered, however, that the Li et al. (2001) and Alarcón-Herrera et al. (2001) studies reported fracture increases (although imprecise with wide confidence intervals) between 1 and 4 mg/L, giving support to a continuous exposure-effect gradient in this range.

### Skeletal Fluorosis

Excessive intake of fluoride will manifest itself in a musculoskeletal disease with a high morbidity. This pathology has generally been termed skeletal fluorosis. Four stages of this affliction have been defined, including a preclinical stage and three clinical stages that characterize the severity. The preclinical stage and clinical stage I are composed of two grades of increased skeletal density as judged by radiography, neither of which presents with significant clinical symptoms. Clinical stage II is associated with chronic joint pain, arthritic symptoms, calcification of ligaments, and osteosclerosis of cancellous bones. Stage III has been termed “crippling” skeletal fluorosis because mobility is significantly affected as a result of excessive calcifications.
in joints, ligaments, and vertebral bodies. This stage may also be associated with muscle wasting and neurological deficits due to spinal cord compression. The current MCLG is based on induction of crippling skeletal fluorosis (50 Fed. Reg. 20164 [1985]). Because the symptoms associated with stage II skeletal fluorosis could affect mobility and are precursors to more serious mobility problems, the committee judges that stage II is more appropriately characterized as the first stage at which the condition is adverse to health. Thus, this stage of the affliction should also be considered in evaluating any proposed changes in drinking-water standards for fluoride.

Descriptions of skeletal fluorosis date back to the 1930s, when the pathology was first recognized in India in areas of endemic fluoride exposure (Shortt et al. 1937) and in occupationally exposed individuals in Denmark (Roholm 1937). From an epidemiological standpoint, few cases of clinical skeletal fluorosis have been documented in the United States. Stevenson and Watson (1957) performed a large retrospective study involving 170,000 radiologic examinations in people from Texas and Oklahoma, where many communities have fluoride water concentrations above 4 mg/L. They radiographically diagnosed only 23 cases of fluoride osteosclerosis in people consuming fluoride at 4 to 8 mg/L and no cases in people exposed to less (the number of people exposed in these categories was not provided). The cases (age 44 to 85) did not have unusual amounts of arthritis or back stiffness given their age (details not provided). Eleven had bone density of an extreme degree, and nine had more than minimal calcification of pelvic ligaments. The authors found no relationship between radiographic findings and clinical diagnosis or symptoms (details not provided). Cases were not classified as to the stage of the fluorosis (using the scheme discussed earlier). Based on the information in the paper, the committee could not determine whether stage II fluorosis was present. In a study of 253 subjects, Leone et al. (1955a) reported increased bone density and coarsened trabeculation in residents of a town with fluoride at 8 mg/L relative to another town with fluoride at 0.4 mg/L. Radiographic evidence of bone changes occurred in 10% to 15% of the exposed residents and was described as being slight and not associated with other physical findings except enamel mottling. The high-fluoride town was partially defluoridated in March 1952 (Maier 1953; Leone et al. 1954a,b; 1955b), a detail not mentioned in the radiographic study (Leone

1The number of patients represented by the 170,000 radiological examinations is not given.

2Maier (1953) indicates that “regular operation” of the defluoridation plant began March 11, 1952. At least one small pilot plant was operated for an unspecified period prior to that date (Maier 1953). Leone et al. (1954a,b) indicated initial defluoridation to 1.2 mg/L. Likins et al. (1956) reported a mean daily fluoride content of treated water in Bartlett of 1.32 mg/L over the first 113 weeks (27 months), with average monthly fluoride concentrations of 0.98-2.13 mg/L over the 18-month period referred to by Leone et al. (1954a,b; 1955b).
et al. 1955a) but which could have affected its results and interpretation. Leone et al. (1954a,b; 1955b) state that “any significant physiological manifestations of prolonged exposure would not be expected to have regressed materially in the 18 months of partial defluoridation.” However, Likins et al. (1956) reported that urinary fluoride concentrations in males fell from means of 6.5 (children) and 7.7 (adults) mg/L before defluoridation to 4.9 and 5.1 mg/L, respectively, after 1 week, 3.5 and 3.4 mg/L, respectively, after 39 weeks, and 2.2 and 2.5 mg/L, respectively, after 113 weeks. These results indicate that, following defluoridation of the water supply, substantial changes in fluoride balance were occurring in the residents, including the apparent remobilization of fluoride from bone.

In patients with reduced renal function, the potential for fluoride accumulation in the skeleton is increased (see Chapter 3). It has been known for many years that people with renal insufficiency have elevated plasma fluoride concentrations compared with normal healthy persons (Hanhijärvi et al. 1972) and are at a higher risk of developing skeletal fluorosis (Juncos and Donadio 1972; Johnson et al. 1979). In cases in which renal disease and skeletal fluorosis were simultaneously present, it still took high concentrations of fluoride, such as from daily ingestion of 4 to 8 L of water containing fluoride at 2 to 3 mg/L (Sauerbrunn et al. 1965; Juncos and Donadio 1972), at least 3 L/day at 2 to 3 mg/L (Johnson et al. 1979), or 2 to 4 L/day at 8.5 mg/L (Lantz et al. 1987) to become symptomatic.

Most recently, the Institute of Medicine evaluated fluoride intake and skeletal fluorosis and was able to find only five reported cases of individuals with stage III skeletal fluorosis in the United States from approximately 1960 to 1997 (IOM 1997). Interestingly, however, a recent report has documented an advanced stage of skeletal fluorosis in a 52-year-old woman consuming 1 to 2 gal of double-strength instant tea per day throughout her adult life (Whyte et al. 2005). Her total fluoride intake was estimated at 37 to 74 mg/day from exposure to fluoride from well water (up to 2.8 mg/L) and instant tea. The report also documented the fluoride content of commercial instant teas and found substantial amounts in most brands. This illustrates the possibility that a combination of exposures can lead to higher than expected fluoride intake with associated musculoskeletal problems. Another case, documented by Felsenfeld and Roberts (1991), indicates the development of skeletal fluorosis from consumption of well water containing fluoride at 7 to 8 mg/L for 7 years. Renal insufficiency was not a factor in this case, but water consumption was considered likely to have been “increased” because of hot weather. Both cases mention joint stiffness or pain, suggesting at least stage II skeletal fluorosis.

From reports from the 1950s through the 1980s, it appears that preclinical bone changes and symptoms of clinical stages I and II may occur with bone concentrations between 3,500 and 12,900 mg/kg (Franke et al.
1975; Dominok et al. 1984; Krishnamachari 1986). The Public Health Service (PHS 1991) has reported that patients with preclinical skeletal fluorosis have fluoride concentrations between 3,500 and 5,500 mg/kg by ash weight. Clinical stage I patients have concentrations in the range of 6,000 to 7,000 mg/kg, stage II patients range from 7,500 to 9,000 mg/kg, and stage III patients have fluoride concentrations of 8,400 mg/kg and greater.\(^3\)

However, a broader review of the literature on bone fluoride concentrations in patients with skeletal fluorosis revealed wider and overlapping ranges associated with different stages of the condition. Tables 5-6 and 5-7 show the reported concentrations of fluoride in bone ash and in bone (dry fat-free material) in cases of skeletal fluorosis. Most authors reported ash concentrations; others reported the dry weight concentrations or both types of results. Because ash contents (fraction of bone remaining in the ash) range widely,\(^4\) the committee did not convert dry weight concentrations to ash concentrations. As reported ranges for various bones in individuals can differ, the tables list the type of bone sampled, distinguishing between measurements of iliac crest or pelvis and other bones.

On the basis of data on fluoride in the iliac crest or pelvis, fluoride concentrations of 4,300 to 9,200 mg/kg in bone ash have been found in cases of stage II skeletal fluorosis, and concentrations of 4,200 to 12,700 mg/kg in bone ash have been reported in cases of stage III fluorosis. The overall ranges for other bones are similar. These ranges are much broader than those indicated by PHS (1991). Baud et al. (1978) showed an overlap in the fluoride content in iliac crest samples between their controls (mean 1,036 mg/kg, range <500 to >2,500) and their cases (mean 5,617 mg/kg, range <2,500 to >10,000). The above ranges overlap the measurements reported by Zipkin et al. (1958), for which no evidence of fluorosis was reported (4,496 ± 2015 and 6,870 ± 1629 mg/kg ash in iliac crest at 2.6 and 4 mg/L, respectively). The expected degree of skeletal fluorosis was not found in two small groups of patients dialyzed with fluoride-containing water, who accumulated average bone-ash fluoride concentrations of 5,000 mg/kg and 7,200 mg/kg (Erben et al. 1984). Some of the cases with the lowest values (e.g., Teotia and Teotia 1973; Pettifor et al. 1989) were known to have hypocalcemia or secondary hyperparathyroidism; many of the industrial case reports described no hypocalcemia. Thus, it appears that fluoride content in bone may be a marker of the risk of skeletal fluorosis. In other words, the likelihood and severity of clinical skeletal fluorosis increase with the

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\(^3\)According to the sources cited by PHS (1991), these concentrations are based on measurements in iliac crest samples.

\(^4\)From 38% to 60%, calculated from 100% minus the reported fraction lost during ashing (Franke and Auerman 1972); (41.8% standard error 1.94%) for the affected group and 49.9% (standard error 5.34%) for the control group (Krishnamachari 1982); and 32.7% to 68.4% (Zipkin et al. 1958).
TABLE 5-6 Reported Concentrations of Fluoride in Bone Ash in Cases of Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Stage of Skeletal Fluorosis</th>
<th>Fluoride Concentration in Bone Ash, mg/kg in Bone Ash</th>
<th>Number of Individuals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preclinical stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vague symptoms</td>
<td>4,100</td>
<td>2</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td></td>
<td>4,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vague symptoms</td>
<td>3,500 to 4,500</td>
<td>Authors’ summary</td>
<td></td>
</tr>
<tr>
<td>Stage 0 to 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0 to I</td>
<td>5,000</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage 0 to I</td>
<td>6,900 (mean)</td>
<td>2</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage 0 to I</td>
<td>5,000 to 5,500</td>
<td>Authors’ summary</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>6,000</td>
<td>2</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td></td>
<td>6,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>5,200 (mean)</td>
<td>8</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage I</td>
<td>6,000 to 7,000</td>
<td>Authors’ summary</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second phase</td>
<td>9,200</td>
<td>1</td>
<td>Roholm 1937</td>
</tr>
<tr>
<td>Stage I to II</td>
<td>8,700</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage II</td>
<td>7,700</td>
<td>2</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td></td>
<td>7,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>7,500 (mean)</td>
<td>9</td>
<td>Franke et al. 1975</td>
</tr>
<tr>
<td>Stage II</td>
<td>7,500 to 9,000</td>
<td>Authors’ summary</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>4,300</td>
<td>4,700&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Stage II</td>
<td>8,800</td>
<td>8,900&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Stage II</td>
<td>2,900 to 4,400</td>
<td>1</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third phase</td>
<td>7,600 to 13,100</td>
<td>1</td>
<td>Roholm 1937</td>
</tr>
<tr>
<td>Stage 3</td>
<td>6,300</td>
<td>1</td>
<td>Singh and Jolly 1961</td>
</tr>
<tr>
<td>Stage III</td>
<td>11,500</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Crippling fluorosis</td>
<td>4,200</td>
<td>1</td>
<td>Teotia and Teotia 1973</td>
</tr>
<tr>
<td>Stage III</td>
<td>8,400</td>
<td>1</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage III</td>
<td>&gt;10,000</td>
<td>Authors’ summary</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 2,500 to 5,000

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TABLE 5-6 Continued

<table>
<thead>
<tr>
<th>Stage of Skeletal Fluorosis</th>
<th>Fluoride Concentration in Bone Ash, mg/kg in Bone Ash</th>
<th>Number of Individuals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Iliac Crest or Pelvis</td>
<td>10,000</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other Bones</td>
<td>9,000 to 11,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>9,100</td>
<td>1</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Other Bones</td>
<td>4,200 to 11,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>12,700</td>
<td>1</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Other Bones</td>
<td>7,600 to 12,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>8,600a</td>
<td>1</td>
<td>Dominok et al. 1984</td>
</tr>
<tr>
<td>Other Bones</td>
<td>8,500 to 12,400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stage not given, or range of stages

| Skeletal fluorosis          | 700 to 6,800 (mean, 3,430) | 10 | Singh and Jolly 1961; see also Singh et al. 1961 |
| Old fluorosis, 7 years without fluoride exposure | 3,000 | 1 | Franke and Auermann 1972 |

| Skeletal fluorosis          | 2,650 | 4 | Teotia and Teotia 1973 |
| Endemic genu valgum         | 3,780 | 43 (54 samples) | Baud et al. 1978; Boillat et al. 1980 |
| Endemic genu valgum         | 4,750 | 20 (37 samples) | Krishnamachari 1982 |
| Endemic genu valgum         | 5,850 | 43 (54 samples) | Boivin et al. 1986 |
| Endemic genu valgum         | 5,617 (2,143)c | 43 (54 samples) | Boivin et al. 1988 (summary of studies) |
| Endemic genu valgum         | 7,283 (416)d | 20 (37 samples) | Boivin et al. 1989; 1990 f |

| Skeletal fluorosis          | 4,200 to 10,100 | 9 | Boivin et al. 1986 |
| Skeletal fluorosis          | 13,300 (2,700)c | 6 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 8,900 (3,400)c | 5 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 6,900 (1,900)c | 13 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 5,600 (2,100)c | 54 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 6,600 (2,700)c | 4 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 7,600 (4,800)c | 14 | Boivin et al. 1988 (summary of studies) |
| Skeletal fluorosis          | 7,900 (3,600)c (range: 4,200 to 22,000) | 29 | Boivin et al. 1989; 1990 f |

| Admitted to hospital for skeletal pain or skeletal deformities | 5,580 (980)c (range: 4,430 to 6,790) | 7 | Pettifor et al. 1989 |

aSamples from right and left sides in same individual.
bTibia or iliac crest; includes 1 case of stage III fluorosis listed separately above.
cIndicates mean and standard deviation.
dIndicates mean and standard error.
eIncludes some studies (or individuals from studies) listed separately above.
fProbably includes individuals from other studies listed above.
TABLE 5-7 Reported Concentrations of Fluoride in Bone (Dry Fat-Free Material) in Cases of Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Stage of Skeletal Fluorosis</th>
<th>Fluoride Concentration in Bone, mg/kg in Dry Fat-Free Material</th>
<th>Number of Individuals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vague symptoms</td>
<td>1,700 and 2,100</td>
<td>2</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage 0 to I</td>
<td>1,900</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage 0 to I</td>
<td>3,000 (mean)</td>
<td>5</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>5,000 to 7,000</td>
<td>1</td>
<td>Wolff and Kerr 1938 (cited in Jackson and Weidmann 1958)</td>
</tr>
<tr>
<td>Early</td>
<td>6,260 and 7,200</td>
<td>2</td>
<td>Sankaran and Gadekar 1964</td>
</tr>
<tr>
<td>Stage I</td>
<td>2,300 and 2,900</td>
<td>2</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage I</td>
<td>3,200 (mean)</td>
<td>15</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>7,680</td>
<td>1</td>
<td>Sankaran and Gadekar 1964</td>
</tr>
<tr>
<td>Stage I to II</td>
<td>4,300</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage II</td>
<td>4,100 and 4,600</td>
<td>2</td>
<td>Franke and Auermann 1972</td>
</tr>
<tr>
<td>Stage II</td>
<td>3,000 (mean)</td>
<td>18</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal fluorosis</td>
<td>8,600</td>
<td>1</td>
<td>Sankaran and Gadekar 1964</td>
</tr>
<tr>
<td>Advanced</td>
<td>8,800 and 9,680</td>
<td>2</td>
<td>Sankaran and Gadekar 1964</td>
</tr>
<tr>
<td>Stage III</td>
<td>3,600 (mean)</td>
<td>4</td>
<td>Schlegel 1974</td>
</tr>
<tr>
<td>Stage not given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old fluorosis, 7 years without fluoride exposure</td>
<td>1,700</td>
<td>1</td>
<td>Franke and Auermann 1972</td>
</tr>
</tbody>
</table>
bone fluoride content, but a given concentration of bone fluoride does not necessarily correspond to a certain stage of skeletal fluorosis in all cases. Other factors (e.g., calcium intake) appear to influence fluorosis severity at different concentrations of bone fluoride.

Overall, the committee finds that the predicted bone fluoride concentrations that can be achieved from lifetime exposure to fluoride at 4 mg/L (10,000 to 12,000 mg/kg bone ash) fall within or exceed the ranges of concentrations that have been associated with stage II and stage III skeletal fluorosis. Based on the existing epidemiologic literature, stage III skeletal fluorosis appears to be a rare condition in the United States. As discussed above, the committee judges that stage II skeletal fluorosis is also an adverse health effect. However, the data are insufficient to provide a quantitative estimate of the risk of this stage of the affliction. The committee could not determine from the existing epidemiologic literature whether stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L. The condition does not appear to have been systematically investigated in recent years in U.S. populations that have had long-term exposures to high concentrations of fluoride in drinking water. Thus, research is needed on clinical stage II and stage III skeletal fluorosis to clarify the relationship of fluoride ingestion, fluoride concentration in bone, and clinical symptoms.

EFFECT OF FLUORIDE ON CHONDROCYTE METABOLISM AND ARTHRITIS

The two key chondrocyte cell types that are susceptible to pathological changes are articular chondrocytes in the joint and growth plate chondrocytes in the developing physis. The medical literature on fluoride effects in these cells is sparse and in some cases conflicting.

From physical chemical considerations, it might be expected that mineral precipitates containing fluoride would occur in a joint if concentrations of fluoride and other cations (such as Ca$^{2+}$) achieved a high enough concentration. A single case report by Bang et al. (1985) noted that a 74-year-old female who was on fluoride therapy for osteoporosis for 30 months had a layer of calcified cartilage containing 0.39% fluoride (or 3,900 mg/kg) by ash weight in her femoral head. The calcification was also visible on x-ray. Unfortunately, the limitation of this observation in a single patient is the lack of information on the preexistence of any calcified osteophytes. Nevertheless, it does indicate that at high therapeutic doses fluoride can be found in mineralizing nodules in articular cartilage.

Studies evaluating patient groups with a greater number of subjects found that the use of fluoride at therapeutic doses in rheumatoid patients showed a conflicting result. In one report (Duell and Chesnut 1991), fluoride exacerbated symptoms of rheumatoid arthritis, but, in another case
(Adachi et al. 1997), it was “well tolerated” with no evidence of worsening of the arthritis. No indications from either study implied that fluoride had a causal relationship with the rheumatoid arthritis. Perhaps the only study in the literature that attempts to link fluoride exposure to the induction of arthritis (osteoarthritis) is from Savas et al. (2001), who indicated that Turkish patients with demonstrated endemic fluorosis had a greater severity of osteoarthritic symptoms and osteophyte formation than age- and sex-matched controls.

The veterinary literature also contains a report indicating that, in 21 dairy herds consuming fluoride-containing feed and water, of the 100 cows examined and determined to have arthritic changes, the bone fluoride concentrations ranged from 2,000 to 8,000 mg/kg (Griffith-Jones 1977).

There are no data from which a dose-response relationship can be drawn regarding fluoride intake and arthritis in humans. However, in a rat study, Harbrow et al. (1992) showed articular changes with fluoride at 100 mg/L in drinking water but no effect at 10 mg/L. The changes with fluoride at 100 mg/L were a thickening of the articular surface (rather than a thinning as would be expected in arthritis) and there were no effects on patterns of collagen and proteoglycan staining. There are no comprehensive reports on the mechanism of fluoride effects in articular chondrocytes in vitro.

The effect of fluoride on growth plate chondrocytes is even less well studied than the effect on articular chondrocytes. It has been demonstrated that chronic renal insufficiency in a rat model can increase the fluoride content in the growth plate and other regions of bone (Mathias et al. 2000); however, this has not been known to occur in humans. Fluoride has also been shown to negatively influence the formation of mineral in matrix vesicles at high concentrations. Matrix vesicles are the ultrastructural particles responsible for initiating mineralization in the developing physis (Sauer et al. 1997). This effect could possibly account, in part, for the observation that fluoride may reduce the thickness of the developing growth plate (Mohr 1990).

In summary, the small number of studies and the conflicting results regarding the effects of fluoride on cartilage cells of the articular surface and growth plate indicate that there is likely to be only a small effect of fluoride at therapeutic doses and no effect at environmental doses.

**FINDINGS**

Fluoride is a biologically active ion with demonstrable effects on bone cells, both osteoblasts and osteoclasts. Its most profound effect is on osteoblast precursor cells where it stimulates proliferation both in vitro and in vivo. In some cases, this is manifested by increases in bone mass in vivo.
The signaling pathways by which this agent works are slowly becoming elucidated.

Life-long exposure to fluoride at the MCLG of 4 mg/L may have the potential to induce stage II or stage III skeletal fluorosis and may increase the risk of fracture. These adverse effects are discussed separately below.

The current MCLG was designed to protect against stage III skeletal fluorosis. As discussed above, the committee judges that stage II is also an adverse health effect, as it is associated with chronic joint pain, arthritic symptoms, slight calcification of ligaments, and osteosclerosis of cancellous bones. The committee found that bone fluoride concentrations estimated to be achieved from lifetime exposure to fluoride at 2 mg/L (4,000 to 5,000 mg/kg ash) or 4 mg/L (10,000 to 12,000 mg/kg ash) fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis (4,300 to 9,200 mg/kg ash and 4,200 to 12,700 mg/kg ash, respectively). This suggests that fluoride at 2 or 4 mg/L might not protect all individuals from the adverse stages of the condition. However, this comparison alone is not sufficient evidence to conclude that individuals exposed to fluoride at those concentrations are at risk of stage II skeletal fluorosis. There is little information in the epidemiologic literature on the occurrence of stage II skeletal fluorosis in U.S. residents, and stage III skeletal fluorosis appears to be a rare condition in the United States. Therefore, more research is needed to clarify the relationship between fluoride ingestion, fluoride concentrations in bone, and stage of skeletal fluorosis before any firm conclusions can be drawn.

Although a small set of epidemiologic studies were useful for evaluating bone fracture risks from exposure to fluoride at 4 mg/L in drinking water, there was consistency among studies using ecologic exposure measures to suggest the potential for an increased risk. The one study using serum fluoride concentrations found no appreciable relationship to fractures. Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to shown an association might have been diminished. Biochemical and physiological data indicate a biologically plausible mechanism by which fluoride could weaken bone. In this case, the physiological effect of fluoride on bone quality and risk of fracture observed in animal studies is consistent with the observational evidence. Furthermore, the results of the randomized clinical trials were consistent with the observational studies. In addition, a dose-response relationship is indicated. On the basis of this information, all members of the committee agreed that there is scientific evidence that under certain conditions fluoride can weaken bone and increase the risk of fractures. The majority of the committee concluded that lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure at 1 mg/L, particularly in some
susceptible demographic groups that are more prone to accumulate fluoride in their bones. However, three of the 12 members judged that the evidence only supported a conclusion that the MCLG might not be protective against bone fracture. They judge that more evidence that bone fractures occur at an appreciable frequency in human populations exposed to fluoride at 4 mg/L is needed before drawing a conclusion that the MCLG is likely to be not protective.

Few studies have assessed fracture risk in populations exposed to fluoride at 2 mg/L in drinking water. The best available study was from Finland, which provided data that suggested an increased rate of hip fracture in populations exposed to fluoride at >1.5 mg/L. However, this study alone is not sufficient to determine the fracture risk for people exposed to fluoride at 2 mg/L in drinking water. Thus, the committee finds that the available epidemiologic data for assessing bone fracture risk in relation to fluoride exposure around 2 mg/L are inadequate for drawing firm conclusions about the risk or safety of exposures at that concentration.

RECOMMENDATIONS

• A more complete analysis of communities consuming water with fluoride at 2 and 4 mg/L is necessary to assess the potential for fracture risk at those concentrations. These studies should use a quantitative measure of fracture such as radiological assessment of vertebral body collapse rather than self-reported fractures or hospital records. Moreover, if possible, bone fluoride concentrations should be measured in long-term residents.
• The effects of fluoride exposure in bone cells in vivo depend on the local concentrations surrounding the cells. More data are needed on concentration gradients during active remodeling. A series of experiments aimed at quantifying the graded exposure of bone and marrow cells to fluoride released by osteoclastic activity would go a long way in estimating the skeletal effects of this agent.
• A systematic study of stage II and stage III skeletal fluorosis should be conducted to clarify the relationship of fluoride ingestion, fluoride concentration in bone, and clinical symptoms. Such a study might be particularly valuable in populations in which predicted bone concentrations are high enough to suggest a risk of stage II skeletal fluorosis (e.g., areas with water concentrations of fluoride above 2 mg/L).
• More research is needed on bone concentrations of fluoride in people with altered renal function, as well as other potentially sensitive populations (e.g., the elderly, postmenopausal women, people with altered acid-balance), to better understand the risks of musculoskeletal effects in these populations.
Reproductive and Developmental Effects of Fluoride

This chapter provides an update on studies of the reproductive and developmental effects of fluoride published since the earlier NRC (1993) review. Studies on reproductive effects are summarized first, primarily covering structural and functional alterations of the reproductive tract. This is followed by a discussion of developmental toxicity in animal and human studies.

REPRODUCTIVE EFFECTS

More than 50 publications since 1990 have focused on the reproductive effects of fluoride. Most of the studies used animal models, primarily rodents, and evaluated structural or functional alterations in the male reproductive tract associated with fluoride. Fewer animal studies evaluated the effects of fluoride on female reproductive tract structure or function. In this section, reports of fluoride effects on reproduction in animal models are reviewed first, followed by a discussion of the available studies of humans.

Animal Studies

The large number of studies gleaned from a search of the literature since 1990 that evaluated reproductive tract structure or function in animal models are outlined in Table 6-1, listing the fluoride dosing regimens and main observations. Most of the studies were conducted for the purpose of hazard identification and involved high doses of fluoride to reveal potentially sensitive reproductive-tract targets and pathways. A few selected
<table>
<thead>
<tr>
<th>Species, Sex, Number</th>
<th>Exposure Route</th>
<th>Concentration/ Dose</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice, F, 15/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Decreased protein in liver, muscle, and small intestine were observed. Significant accumulation of glycogen in gastrocnemius muscle and liver. Decline in succinate dehydrogenase activity in pectoralis muscle of treated mice. Administration of ascorbic acid and calcium to NaF-treated mice caused significant recovery from fluoride toxicity.</td>
<td>Chinoy et al. 1994</td>
</tr>
<tr>
<td>Mice, F, 25/group</td>
<td>Orally, feeding tube attached to hypodermic syringe</td>
<td>5 mg/kg/day (NaF)</td>
<td>45 days</td>
<td>Fluoride concentrations were increased in the urine, serum, and ovary compared with controls. In the ovary, there was impaired production of glutathione and impaired function of the protective enzymes—namely, glutathione peroxidase, superoxide dismutase, and catalase. There was increased ovarian lipid peroxidation. Enhanced concentrations of potassium and sodium were observed in the serum. The concentrations of serum calcium showed significant depletion. Withdrawal of NaF for 45 days showed partial recovery. Recovery was enhanced by treatment with ascorbic acid, calcium, vitamin E, and vitamin D.</td>
<td>Chinoy and Patel 1998</td>
</tr>
<tr>
<td>Mice, F, 20/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Significant decline of ovarian protein and 3β- and 17β-hydroxysteroid dehydrogenase activities. Hypcholesterolemic effect in serum detected. Accumulation of glycogen in uterus.</td>
<td>Chinoy and Patel 2001</td>
</tr>
<tr>
<td>Species, Sex, Number</td>
<td>Exposure Route</td>
<td>Concentration/Dose</td>
<td>Exposure Duration</td>
<td>Effects</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
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<td>---------</td>
<td></td>
</tr>
<tr>
<td>Mice, F, 15/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Decreased protein in liver, muscle, and small intestine were observed. Significant accumulation of glycogen in uterus. Administration of ascorbic acid and calcium to NaF-treated mice caused significant recovery from fluoride toxicity.</td>
<td></td>
</tr>
<tr>
<td>Mice, F, 25/group</td>
<td>Orally, feeding tube attached to hypodermic syringe</td>
<td>5 mg/kg/day (NaF)</td>
<td>45 days</td>
<td>Fluoride concentrations were increased in the urine, serum, and ovary compared with controls. In the ovary, there was a decrease in proteins and β-hydroxysteroid dehydrogenase activities. Recovery was enhanced by vitamin E treatment. Recovery was enhanced by treatment with ascorbic acid, calcium, vitamin E, and vitamin D.</td>
<td></td>
</tr>
<tr>
<td>Mice, M, 20/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Significant decline of ovarian protein and β- and 17β-hydroxysteroid dehydrogenase activities. Hypocholesterolemic effect in serum detected. Accumulation of glycogen in uterus.</td>
<td></td>
</tr>
<tr>
<td>Mice, M, 40/group</td>
<td>Drinking water</td>
<td>10, 20 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Epithelial-cell pyknosis and absence of luminal sperm were observed. Disorganization of germinal epithelial cells of seminiferous tubules with absence of sperm in the lumina. Reduction in denudation of cells, epithelial cell height, nuclear pyknosis, and absence of sperm observed in the cauda epididymis. The vas deferens epithelium showed clumped sterecilia, nuclear pyknosis, and cell debris but no sperm in the lumen and an increase in the lamina propria. Marked recovery was observed with withdrawal of treatment. No effects observed in the prostate gland or seminal vesicles.</td>
<td></td>
</tr>
<tr>
<td>Mice, M, 20/group</td>
<td>Gavage</td>
<td>10, 20 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>NaF caused lessened fertility rate when normal cycling female mice were mated with treated mice. Large numbers of deflagellated spermatozoa with acrosomal, midpiece, and tail abnormalities were observed. Significant recovery in sperm count, sperm motility, and fertility rate was observed after withdrawal of treatment for 2 months.</td>
<td></td>
</tr>
<tr>
<td>Mice, M, 20/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Alterations in epididymal milieu as elucidated by the significant decrease in concentrations of sialic acid and protein as well as activity of ATPase in epididymides. Significant decrease in body and epididymis weight. Weight of vas deferens and seminal vesicle were not affected. Sperm maturation process was affected, leading to decline in cauda epididymal sperm motility and viability. Significant reduction in fertility rate and cauda epididymal sperm count. Treatment induced substantial metabolic alterations in the epididymides, vas deferens, and seminal vesicles of mice. Supplements of vitamin D and E during the withdrawal period enhanced recovery of all NaF-induced effects.</td>
<td></td>
</tr>
<tr>
<td>Species, Sex, Number</td>
<td>Exposure Route</td>
<td>Concentration/Dose</td>
<td>Exposure Duration</td>
<td>Effects</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Mice, M, 20/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Significant decline in sperm acrosomal acrosin and hyaluronidase. Acrosomal damage and deflagellation observed. Sperm nuclear integrity not affected. Structural and metabolic alterations and reduced activity of the enzymes in sperm resulted in a significant decrease in sperm count and poor fertility rate. Cessation of NaF treatment for 30 days did not bring about complete recovery. Administration of ascorbic acid or calcium enhanced recovery and was more pronounced in groups treated with both ascorbic acid and calcium.</td>
<td>Chinoy and Sharma 2000</td>
</tr>
<tr>
<td>Mice, M, 10/group</td>
<td>Drinking water</td>
<td>100, 200, 300 mg/L (NaF)</td>
<td>4 and 10 weeks</td>
<td>Mean doses during 4-week treatment: 12.53, 21.80, 39.19 mg/kg/day. Mean doses during 10-week treatment: 8.85, 15.64, and 27.25 mg/kg/day</td>
<td>Mean doses during 4-week treatment: 12.53, 21.80, 39.19 mg/kg/day. Mean doses during 10-week treatment: 8.85, 15.64, and 27.25 mg/kg/day.</td>
</tr>
<tr>
<td>Rat, F, 25 (treated), 18 (control)</td>
<td>Drinking water</td>
<td>150 mg/L (NaF)</td>
<td>From 60 days before mating and through pregnancy and lactation</td>
<td>There was inhibition of lactation in rats with chronic fluorosis, as measured by slower rates of body weight gain in pups. This was associated with a marked decrease in milk production in lactating rat dams. Granulation and thickening of the mammary gland stroma were observed. The secretory activity of the lactotrophs was reduced, with smaller, less dense secretory granules and an increase in the number of large mature secretory granules. The appearance of extremely large abnormal secretory granules in lactotroph cytoplasma was noted.</td>
<td>Yuan et al. 1994</td>
</tr>
<tr>
<td>Rat, F, 33-35/group</td>
<td>Drinking water</td>
<td>10, 25, 100, 175, 250 mg/L (NaF)</td>
<td>Mean doses: 1.4, 3.9, 15.6, 24.7, and 25.1 mg/kg/day (NaF)</td>
<td>From day of sperm detection to gestation day 20.</td>
<td>Mean doses: 1.4, 3.9, 15.6, 24.7, and 25.1 mg/kg/day (NaF)</td>
</tr>
<tr>
<td>Rat, F, 10/group</td>
<td>Drinking water</td>
<td>200, 400, and 600 mg/L (NaF)</td>
<td>Mean doses: 22.58, 18.35, and 28.03 mg/kg/day (NaF)</td>
<td>30 days, before mating</td>
<td>Mean doses: 22.58, 18.35, and 28.03 mg/kg/day (NaF)</td>
</tr>
<tr>
<td>Rat, F, 10/group</td>
<td>Gavage</td>
<td>40 mg/kg/day (NaF)</td>
<td>Days 6 to 19 of gestation</td>
<td>Significant reductions in body weight, feed consumption, absolute uterine weight, and number of implantations. Administration of vitamin E or calcium enhanced recovery and was more pronounced in groups treated with both ascorbic acid and calcium.</td>
<td>Vitamin E also had that effect but was not as great as vitamin C.</td>
</tr>
<tr>
<td>Species, Sex, Number</td>
<td>Exposure Route</td>
<td>Concentration/Dose</td>
<td>Exposure Duration</td>
<td>Effects</td>
<td>Reference</td>
</tr>
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<td>-----------</td>
</tr>
<tr>
<td>Mice, M, 10/group</td>
<td>Drinking water</td>
<td>10, 25, 100, 175, 250 mg/L (NaF)</td>
<td>Mean doses: 1.4, 3.9, 15.6, 24.7, and 25.1 mg/kg/day (NaF)</td>
<td>From day of sperm detection to gestation day 20.</td>
<td>Significant reductions in maternal water consumption in the two highest dose groups and a significant reduction in maternal feed consumption in the high-dose group. Body weights of dams were reduced in the higher-dose groups. No significant effect on any reproductive end points. Developmental effects of fluoride were minimal, with 250 mg/L (25.1 mg/kg/day being the lowest observed effect level due to skeletal variations).</td>
</tr>
<tr>
<td>Rat, F, 25 (treated), 18 (control)</td>
<td>Drinking water</td>
<td>150 mg/L (NaF)</td>
<td>From 60 days before mating and through pregnancy and lactation</td>
<td>There was inhibition of lactation in rats with chronic fluorosis, as measured by slower rates of body weight gain in pups and lower amount of milk suckled in 30 minutes compared with control pups. Prolactin concentration was decreased in serum but increased in the pituitary gland. Microscopic examination showed accumulation of large mature secretory granules and appearance of extremely large abnormal secretory granules in lactotroph cytoplasm.</td>
<td>Yuan et al. 1994</td>
</tr>
<tr>
<td>Rat, F, 33-35/group</td>
<td>Drinking water</td>
<td>200, 400, and 600 mg/L (NaF)</td>
<td>Mean doses: 22.58, 18.35, and 28.03 mg/kg/day (NaF)</td>
<td>30 days, before mating</td>
<td>None of the rats in the 28.03 mg/kg/day group survived the study period, and only three survived from the 18.35 mg/kg/day group. Clinical signs of toxicity (dehydration, lethargy, hunched posture) were observed in these groups. All the rats exposed to 22.58 mg/kg/day survived, and showed no signs of toxicity. Fetotoxicity observed at 22.58 mg/kg/day. Reduced number of viable fetuses, increased number of pregnant rats with resorptions, and increased total number of resorptions.</td>
</tr>
<tr>
<td>Rat, F, 10/group</td>
<td>Gavage</td>
<td>40 mg/kg/day (NaF)</td>
<td>Days 6 to 19 of gestation</td>
<td>Significant reductions in body weight, feed consumption, absolute uterine weight, and number of implantations. Significantly higher incidence of skeletal and visceral abnormalities. When NaF was administered with vitamin C, the total percentage of skeletal and visceral abnormalities was significantly lower compared with the group treated with NaF only. Vitamin E also had that effect but was not as great as vitamin C.</td>
<td>Verma and Guna Sherlin 2001</td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th>Species, Sex, Number</th>
<th>Exposure Route</th>
<th>Concentration/Dose</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, M, 15-20/group</td>
<td>Single microdose injection into the vasa deferentia</td>
<td>50 µg/50 µL (NaF)</td>
<td>Single dose injection</td>
<td>Arrest of spermatogenesis and absence of spermatozoa in the lumina of the seminiferous tubules of the testes. This resulted in a decline in sperm count in caudae epididymides. Deflagellation and tail abnormalities were observed.</td>
<td>Chinoy et al. 1991a</td>
</tr>
<tr>
<td>Rat, M, 12/group</td>
<td>Drinking water</td>
<td>5 and 10 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Succinate dehydrogenase activity in the testes, adenosine triphosphatase activity, and sialic acid concentrations in epididymides in testes were inhibited. A more pronounced effect was observed on the cauda epididymis. Testicular cholesterol and serum testosterone concentrations were not affected. Significant decline in fertility attributed to decreased sperm motility and count.</td>
<td>Chinoy et al. 1992</td>
</tr>
<tr>
<td>Rat, M, 14/group</td>
<td>Drinking water</td>
<td>100 and 200 mg/L (NaF)</td>
<td>6 and 16 weeks</td>
<td>Severalfold increase in fluoride concentrations in the testes and bone at both test concentrations compared with controls. Fifty percent of the rats in both treatment groups exhibited histopathologic changes in the germinal epithelium of the testes after 16 weeks. Concentrations of copper and manganese in the testes, liver, and kidneys were not changed. Iron concentrations in the testes and plasma were not affected by fluoride but were increased in the liver, kidneys, and bone. Concentrations of zinc in the testes, plasma, liver, and kidneys decreased significantly, particularly in the 16-week groups. Zinc tended to increase in the bone.</td>
<td>Krasowska and Wlostowski 1992</td>
</tr>
<tr>
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<tr>
<td>Rat, M, 25-30/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>50 days</td>
<td>After 50 days of treatment, sperm acrosomal hyaluronidase and acrosin were reduced. Other observations included acrosomal damage and deflagellation of sperm, decline in sperm motility, decreased cauda epididymal sperm count, and reduced fertility. Incomplete recovery observed at withdrawal of NaF treatment for 70 days. Ascorbic acid and calcium produced significant recovery of NaF-induced effects.</td>
<td>Narayana and Chinoy 1994a</td>
</tr>
<tr>
<td>Rat, M, 10/group</td>
<td>Drinking water, administered before feeding</td>
<td>10 mg/kg/day (NaF)</td>
<td>50 days</td>
<td>No significant change in testicular cholesterol concentrations. Testicular 3β-HSD and 17β-HSD activities were modestly decreased by NaF ingestion. Histomorphometric analyses indicated a significant change in the Leydig cell diameter in correlation with androgen concentrations.</td>
<td>Narayana and Chinoy 1994b</td>
</tr>
<tr>
<td>Rat, M, 10-30/group</td>
<td>Gavage</td>
<td>10 mg/kg/day (NaF)</td>
<td>30 and 50 days</td>
<td>Significant elevation in serum fluoride concentrations (3.6 ± 0.11 ppm) with a simultaneous rise in sperm calcium. Treatment resulted in structural and metabolic alterations in sperm, leading to low sperm motility, low sperm mitochondrial activity index, reduced viability, and changes in sperm membrane phospholipids. A significant reduction in electrolyte concentrations of sperm was observed. Protein concentrations in cauda epididymal sperm suspension, vas deferen, seminal vesicle, and prostate significantly decreased after treatment. Glycogen accumulated in vas deferen and fructose decreased in seminal vesicles and vas deferen.</td>
<td>Chinoy et al. 1995</td>
</tr>
<tr>
<td>Rat, M, 18/group</td>
<td>Drinking water</td>
<td>100, 200 mg/L (NaF)</td>
<td>2, 4, 6 weeks</td>
<td>Serum testosterone concentration decreased with time in exposed rats. Testis cholesterol concentration was significantly decreased in the liver of rats exposed 4 and 6 weeks.</td>
<td>Zhao et al. 1995</td>
</tr>
<tr>
<td>Rat, M, 24/group</td>
<td>Injection, left testis</td>
<td>50, 175, 250 ppm (NaF)</td>
<td>Single injection</td>
<td>Seminiferous tubule damage observed in vehicle-injected control and exposed testes; no damage was observed in noninjected testes. Polymorphonuclear leukocyte infiltration was observed at injection site in both vehicle- and fluoride-injected groups after 24 hours. No effect on Leydig cells.</td>
<td>Sprando et al. 1996</td>
</tr>
</tbody>
</table>

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<tr>
<td>Rat, M, 12/group</td>
<td>Drinking water</td>
<td>25, 100, 175, 200 mg/L (NaF)</td>
<td>14 weeks (10 weeks pretreatment, 3 weeks mating, 1 week postmating)</td>
<td>No effects were observed within the P generation males and the F&lt;sub&gt;1&lt;/sub&gt; generation groups in testis weights, prostate/seminal vesicle weights, nonreproductive organ weights, testicular spermatid counts, sperm production per gram of testis per day, sperm production per gram of testis, lutenizing hormone, follicle-stimulating hormone, or serum testosterone concentrations. No histological changes were observed in testicular tissues from either the P or the F&lt;sub&gt;1&lt;/sub&gt; generation.</td>
<td>Sprando et al. 1997</td>
</tr>
<tr>
<td>Rat, M, 25</td>
<td>Drinking water</td>
<td>25, 100, 175, 250 mg/L (NaF)</td>
<td>In utero, during lactation, 14-weeks post-weaning</td>
<td>No significant effect on absolute volume of the seminiferous tubules, interstitial space, Leydig cells, blood vessel boundary layer, lymphatic space, macrophages, tubular lumen or absolute tubular length and absolute tubular surface area, mean Sertoli cell nucleoli number per tubular cross-section, mean seminiferous tubule diameter, and mean height of the seminiferous epithelium. Statistically significant decrease in the absolute volume and volume percent of the lymphatic endothelium was observed in NaF-treated groups (175 and 250 mg/L) and in the testicular capsule in the NaF-treated group (100 mg/L).</td>
<td>Sprando et al. 1998</td>
</tr>
<tr>
<td>Rat, M, F, 36-48/group</td>
<td>Drinking water</td>
<td>0, 25, 100, 175, 250 mg/L (NaF)</td>
<td>10 weeks</td>
<td>Decreased fluid consumption observed at 175 and 250 mg/L attributed to decreased palatability; no effect on reproduction. No cumulative effects were observed in any generation. Mating, fertility, and survival, organ-to-body weight ratios, and organ-to-brain ratios were not affected. Treatment up to 250 mg/L did not affect reproduction.</td>
<td>Collins et al. 2001a</td>
</tr>
<tr>
<td>Species, Sex, Number</td>
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<tr>
<td>Rat, M, 6/group</td>
<td>Gavage</td>
<td>20 mg/kg/day (NaF)</td>
<td>29 days</td>
<td>Testicular 3β-HSD and 17β-HSD activities were decreased significantly. Substantial reduction in plasma concentrations of testosterone in the exposed group. Decreased epididymal sperm count and fewer mature luminal spermatozoa in the exposed group. NaF treatment was associated with oxidative stress, as indicated by an increased concentration of conjugated dienes in the testis, epididymis, and epididymal sperm pellet. Significant reduction in peroxidase and catalase activities in the sperm pellet in exposed group as compared with controls.</td>
<td>Ghosh et al. 2002</td>
</tr>
<tr>
<td>Rat, M, F, 10/group</td>
<td>Gavage</td>
<td>40 mg/kg/day (NaF)</td>
<td>Day 6 of gestation to day 21 of lactation</td>
<td>NaF treatment associated with significant reductions in body weight, feed consumption, concentration of glucose, and protein in the serum. Administration of vitamins C, D, and E helped to restore body weight loss as well as glucose, protein, sodium, and potassium concentrations in the serum of exposed rats. Withdrawal of NaF treatment during lactation caused significant amelioration in feed consumption and in serum sodium, potassium, glucose, and protein concentrations. Additional treatment with vitamin E caused substantial improvements in body weight reductions and in serum concentration of sodium, potassium, glucose, and protein.</td>
<td>Verma and Guna Sherlin 2002a</td>
</tr>
<tr>
<td>Rabbit, F, 10/group</td>
<td>Subcutaneous injection</td>
<td>5, 10, 20, 50 mg/kg/day (NaF)</td>
<td>100 days</td>
<td>Abnormal accumulation of lipids in testes observed in treated rabbits. Hyperphospholipidemia, hypertriglyceridemia, and hypercholesterolemia indicated enhanced lipid biosynthesis was observed in response to fluoride toxicosis. Significant (P &lt; 0.001) increase in amount of free fatty acids observed in testes of treated animals.</td>
<td>Shashi 1992a</td>
</tr>
<tr>
<td>Rabbit, M, 5/group</td>
<td>Feed</td>
<td>20, 40 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Decline in fertility related to reduced sperm motility and count and changes in morphology and metabolism. No recovery after withdrawal for 30 days from treatment. With administration of ascorbic acid and calcium, marked recovery occurred.</td>
<td>Chinoy et al. 1991b</td>
</tr>
<tr>
<td>Species, Sex, Number</td>
<td>Exposure Route</td>
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<tr>
<td>Rabbit, M, 10/group</td>
<td>Drinking water</td>
<td>10 mg/kg/day (NaF)</td>
<td>18 or 29 months</td>
<td>Loss of cilia on the epithelial cells lining the lumen of the ductuli efferentes of the caput epididymidis and of stereocilia on the epithelial cells lining the lumen of the vas deferens was observed. The boundaries of cells peeled off and were not clear in some regions of the epithelial lining of the lumen of the ductuli efferentes and vas deferens. Cessation of spermatogenesis was noted only in rabbits treated for 29 months.</td>
<td>Susheela and Kumar 1991</td>
</tr>
<tr>
<td>Rabbit, M, 8/group</td>
<td>Drinking water</td>
<td>10 mg/kg/day (NaF)</td>
<td>18 months</td>
<td>Structural defects in the flagellum, the acrosome, and the nucleus of the spermatids and epididymal spermatozoa were observed in the treated rabbits. Absence of outer microtubules, complete absence of axonemes, structural and numeric aberrations of outer dense fibers, breakdown of the fibrous sheath, structural defects in the mitochondria of the middle piece of the flagellum, and detachment and peeling of the acrosome from the flat surfaces of the nucleus was observed.</td>
<td>Kumar and Susheela 1994</td>
</tr>
<tr>
<td>Rabbit, M, 12/group</td>
<td>Drinking water</td>
<td>10 mg/kg/day (NaF)</td>
<td>20 and 23 months</td>
<td>Fluoride concentrations in the sera of treated animals were significantly increased. Loss of stereocilia, significant decrease in the height of the pseudostratified columnar epithelium, and significant increase in the diameter of the caput and cauda ductus epididymis observed in the 23-month treatment group. Weights of the cauda epididymis and caput were significantly reduced in the 23-month-treated animals; the number of secretory granules in these organs was reduced.</td>
<td>Kumar and Susheela 1995</td>
</tr>
<tr>
<td>Species, Sex, Number</td>
<td>Exposition Route</td>
<td>Concentration/Dose</td>
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<td>10 mg/kg/day (NaF)</td>
<td>18 and 23 months</td>
<td>Loss of cilia on the epithelial cells lining the lumen of the ductuli efferentes of the caput epididymidis and of the ductuli efferentes and vas deferens. Cessation of spermatogenesis was noted only in rabbits treated for 29 months.</td>
<td>Susheela and Kumar 1991</td>
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<td>Rabbit, M, 8/group</td>
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<td>18 months</td>
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<td>Kumar and Susheela 1994</td>
</tr>
<tr>
<td>Rabbit, M, 12/group</td>
<td>Drinking water</td>
<td>10 mg/kg/day (NaF)</td>
<td>20 and 23 months</td>
<td>Fluoride concentrations in the sera were significantly increased. Loss of stereocilia, significant decreases in the number of secretory granules in the seminiferous tubules, and decreases in the number of Leydig cells were observed in the 23-month-treated animals; the number of secretory granules in those organs was reduced.</td>
<td>Kumar and Susheela 1995</td>
</tr>
<tr>
<td>Guinea pig, M, 10/group</td>
<td>Gavage</td>
<td>30 mg/kg/day (NaF)</td>
<td>30 days</td>
<td>Structural and metabolic alterations of the cauda epididymal spermatozoa led to substantial decreases in sperm mitochondrial activity index, motility, live/dead ratio. Increases in sperm membrane phospholipids were observed. ATPase, succinate dehydrogenase, and glutathione concentrations were decreased in testis of treated animals. Administration of ascorbic acid led to recovery in these parameters.</td>
<td>Chinoy et al. 1997</td>
</tr>
<tr>
<td>Sheepdog, F, M, 5/group</td>
<td>Feed</td>
<td>460 ppm (fluoride)</td>
<td>2 years</td>
<td>No adverse effect on reproduction attributable to treatment. Bony exostoses was observed in 4 of 10 treated dogs.</td>
<td>Schellenberg et al. 1990</td>
</tr>
</tbody>
</table>

ABBREVIATIONS: F, female; HSD, hydroxysteroid dehydrogenase; M, male.
examples illustrate the results of the many hazard identification studies: (1) cessation of spermatogenesis and alterations in the epididymis and vas deferens were observed in rabbits administered sodium fluoride (NaF) at 10 milligrams per kilogram (mg/kg) of body weight for 29 months (Susheela and Kumar 1991); (2) effects on Leydig cells and decreased serum testosterone were observed in rats exposed to NaF at 10 mg/kg for 50 days (Narayana and Chinoy 1994b); and (3) decreased protein in the ovary and uterus and decreased activity of steroidogenic enzymes (3β-hydroxysteriod dehydrogenase [HSD] and 17β-HSD) was found in mice treated with NaF at 10 mg/kg for 30 days (Chinoy and Patel 2001). In general, the hazard identification studies show that the reproductive tract is susceptible to disruption by fluoride at a concentration sufficiently high to produce other manifestations of toxicity.

For risk evaluation, a comprehensive multigenerational study of fluoride effects on reproduction using standard guidelines and adequate numbers of animals has been conducted in rats (Collins et al. 2001a). Rats were administered drinking water with NaF at 0, 25, 100, 175, and 250 mg/L over three generations. No compound-related effects were found on mating or fertility; gestation or lactation; or F1 survival, development, and organ weights. No alterations in the teeth were seen except for mild whitening observed in rats exposed to fluoride at 100 mg/L or greater. That well-conducted study concluded that NaF at concentrations up to 250 mg/L in the drinking water did not alter reproduction in rats (Collins et al. 2001a).

**Human Studies**

The few studies gleaned from a search of the literature since 1990 that evaluated reproductive effects of fluoride ingestion in humans are outlined in Table 6-2, listing the estimated fluoride exposure and main observations. In highly exposed men with and without skeletal fluorosis (fluoride at 1.5-14.5 mg/L in the drinking water), serum testosterone concentrations were significantly lower than in a control cohort exposed to fluoride at less than 1.0 mg/L in drinking water (Susheela and Jethanandani 1996). Although there was a 10-year difference in the mean ages between the skeletal fluorosis patients (39.6 years) and control subjects (28.7 years), this study suggests that high concentrations of fluoride can alter the reproductive hormonal environment.

In an ecological study of U.S. counties with drinking-water systems reporting fluoride concentrations of at least 3 mg/L (Freni 1994), a decreased fertility rate was associated with increasing fluoride concentrations. Because methods for analyzing the potential amounts and direction of bias in ecological studies are limited, it is possible only to discuss some of the strengths and weaknesses of this complicated study (see Chapter 10 and...
Appendix C for a more in-depth discussion of ecologic bias). Freni’s study is actually partially ecologic; the outcome (fertility) is age-standardized at the individual level, while exposure to fluoride and covariates are measured at the group level. Controlling for age of the mother is a strength of the study, but to avoid bias all ecological variables should be standardized in the same fashion (Greenland 1992). The model adjusted for a number of important socioeconomic and demographic variables at the group level, but these might not adequately control for individual-level determinants of fertility such as family income and use of contraceptives. For example, median income (a group-level variable) and family income (an individual-level variable) may have independent and interactive effects on outcome. One of the two ecologic exposure measures examined the percentage of the population served by water systems with fluoride concentrations of at least 3 mg/L. That has the potential advantage of not assuming an effect at lower fluoride concentrations (as does the mean fluoride concentration, the other exposure measure), but it has the disadvantage that, unlike individual-level studies, nondifferential misclassification of dichotomous exposures within groups tend to bias ecologic results away from the null (Brenner et al. 1992). While the results of the Freni study are suggestive, the relationship between fertility and fluoride requires additional study.

A study of workers in Mexico, who were occupationally exposed to fluoride (estimated to range from 3 to 27 mg/day) producing hydrofluoric acid and aluminum fluoride, found alterations in serum hormone concentrations with normal semen parameters (Ortiz-Perez et al. 2003). However, that study involved a comparison of a high-fluoride-exposed group and a low-fluoride-exposed group with poorly defined exposures and overlapping exposure characteristics.

Overall, the available studies of fluoride effects on human reproduction are few and have significant shortcomings in design and power, limiting inferences.

DEVELOPMENTAL EFFECTS

There is wide variation with some correlation between fluoride concentration in maternal serum and cord blood, indicating that fluoride readily crosses the placenta. In general, average cord blood concentrations are approximately 60% of maternal serum concentrations, with proportionally lesser amounts present as higher maternal serum concentrations (Gupta et al. 1993; Malhotra et al. 1993; Shimonovitz et al. 1995). Therefore, potential toxicity to the developing embryo and fetus in the setting of high maternal ingestion of fluoride has been a concern evaluated in both animal and humans.
### TABLE 6-2 Human Reproductive Studies

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Exposure Route, Duration</th>
<th>Concentration/Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women (n = 25)</td>
<td>Drinking water</td>
<td>Maternal blood fluoride concentrations ranging from 0.1 to 2.4 ppm</td>
<td>Fairly positive correlation ($r = 0.736$) between cord blood values and maternal blood fluoride concentrations. On average, the cord blood fluoride concentration was about 60% that in maternal blood. At a maternal fluoride concentration greater than 0.4 ppm, the cord blood fluoride concentration increased by only about 12%. The placenta was found to serve as an effective barrier within this range.</td>
</tr>
<tr>
<td>Pregnant women (n = 25)</td>
<td>Drinking water</td>
<td>Maternal plasma fluoride concentrations ranging from 0.12 to 0.42 µg/mL</td>
<td>Cord plasma fluoride concentrations ranged from 0.11-0.39 µg/ml. In 8% of the cases, cord plasma concentrations were higher than maternal plasma concentrations. Positive correlation ($r = 0.97$) in fluoride concentrations between maternal and cord plasma indicates that the placenta allowed passive diffusion of fluoride from mother to fetus.</td>
</tr>
<tr>
<td>Pregnant women undergoing amniocentesis (n = 121, divided into 6 exposure groups)</td>
<td>Oral doses, 24 hours and 3 hours before amniocentesis</td>
<td>0.56, 1.12, 1.68, 2.30, or 2.80 mg of NaF corresponding to 0.25, 0.50, 0.75, 1.00, or 1.25 mg of F-</td>
<td>F-concentration in amniotic fluid was significantly higher than controls in the 1.25 mg/day F-group but not in any of the other exposure groups. No significant correlation between F-concentration in maternal plasma and in amniotic fluid.</td>
</tr>
<tr>
<td>Men (ages 28-30; n = 8)</td>
<td>In vitro with spermatozoa, intervals of 5, 10, and 20 minutes</td>
<td>25, 50, 250 mM (NaF)</td>
<td>Substantial enhancement of acid phosphatase and hyaluronidase activities after 5 and 10 minutes ($P &lt; 0.001$). Decrease in lysosomal enzyme activity after 20 minutes. Analysis of sperm revealed elongated heads, deflagellation, splitting, loss of the acrosome, and coiling of the tail. Glutathione concentrations exhibited time-dependent decrease with complete depletion after 20 minutes ($P &lt; 0.001$). Suppressed sperm motility after 20 minutes at a dose of 250 mM ($P &lt; 0.001$).</td>
</tr>
<tr>
<td>30 regions spread over nine states</td>
<td>Drinking water</td>
<td>≥ 3 mg/L (fluoride)</td>
<td></td>
</tr>
<tr>
<td>Pregnant women (n = 22)</td>
<td>Drinking water</td>
<td>Maternal serum fluoride concentrations ranging from 0.003-0.041µg/ml</td>
<td></td>
</tr>
<tr>
<td>Men with skeletal fluorosis (n = 30)</td>
<td>Drinking water</td>
<td>1.5-14.5 mg/L (fluoride)</td>
<td></td>
</tr>
<tr>
<td>Male workers in Mexico (ages 20-50; n = 126), who produce fluorohydric acid and aluminum fluoride</td>
<td>Drinking water</td>
<td>3-27.4 mg/day (fluoride)</td>
<td></td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** FSH, follicle-stimulating hormone.
### Table 6-2: Human Reproductive Studies

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<td>Malhotra et al. 1993</td>
</tr>
<tr>
<td>Pregnant women undergoing amniocentesis (n = 121, divided into 6 exposure groups)</td>
<td>Oral doses, 24 hours and 3 hours before amniocentesis</td>
<td>0.56, 1.12, 1.68, 2.30, or 2.80 mg of NaF corresponding to 0.25, 0.50, 0.75, 1.00, or 1.25 mg of F—</td>
<td>F-concentration in amniotic fluid was significantly higher than controls in the 1.25 mg/day F-group but not in any of the other exposure groups. No significant correlation between F-concentration in maternal plasma and in amniotic fluid.</td>
<td>Brambilla et al. 1994</td>
</tr>
<tr>
<td>Men (ages 28-30; n = 8)</td>
<td>In vitro with spermatozoa, intervals of 5, 10, and 20 minutes</td>
<td>25, 50, 250 mM (NaF)</td>
<td>Substantial enhancement of acid phosphatase and hyaluronidase activities after 5 and 10 minutes ( P &lt; 0.001 ). Decrease in lysosomal enzyme activity after 20 minutes. Analysis of sperm revealed elongated heads, deflagellation, splitting, loss of the acrosome, and coiling of the tail. Glutathione concentrations exhibited time-dependent decrease with complete depletion after 20 minutes ( P &lt; 0.001 ). Suppressed sperm motility after 20 minutes at a dose of 250 mM ( P &lt; 0.001 ).</td>
<td>Chinoy and Narayana 1994</td>
</tr>
<tr>
<td>30 regions spread over nine states</td>
<td>Drinking water ( \geq 3 ) mg/L (fluoride)</td>
<td></td>
<td>In this ecological study, there was an association between decreasing total fertility rate and increasing fluoride concentrations in most regions. Combined result was a negative total fertility rate/fluoride association with a consensus combined ( P ) value of 0.0002-0.0004. Association was based on population means rather than individual women.</td>
<td>Freni 1994</td>
</tr>
<tr>
<td>Pregnant women (n = 22)</td>
<td>Drinking water</td>
<td>Maternal serum fluoride concentrations ranging from 0.003-0.041µg/ml</td>
<td>Cord serum fluoride concentrations ranged from 0.003-0.078 µg/ml, and neonatal serum concentrations ranged from 0.017-0.078 µg/ml. No correlation in fluoride concentrations found between maternal and cord sera, maternal and neonatal sera, or maternal and neonatal sera.</td>
<td>Shimonovitz et al. 1995</td>
</tr>
<tr>
<td>Men with skeletal fluorosis (n = 30)</td>
<td>Drinking water</td>
<td>1.5-14.5 mg/L (fluoride)</td>
<td>Serum testosterone concentrations in patients were significantly lower than controls ( P &lt; 0.01 ).</td>
<td>Susheela and Jethanandani 1996</td>
</tr>
<tr>
<td>Male workers in Mexico (ages 20-50; n = 126), who produce fluorohydric acid and aluminum fluoride</td>
<td>Drinking water</td>
<td>3-27.4 mg/day (fluoride)</td>
<td>In the high-fluoride exposure group, a significant increase in FSH ( P &lt; 0.05 ) and a reduction of inhibin-B, free testosterone, and prolactin in serum ( P &lt; 0.05 ) were observed. Decreased sensitivity was found in the FSH response to inhibin-B ( P &lt; 0.05 ) when the high-exposure group was compared with the low-exposure group. Significant partial correlation was observed between urinary fluoride and serum concentrations of inhibin-B ( P &lt; 0.028 ). No abnormalities were found in the semen parameters in either the high- or low-fluoride exposure groups.</td>
<td>Ortiz-Perez et al. 2003</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** FSH, follicle-stimulating hormone.
Animal Studies

Studies gleaned from a search of the literature since 1990 that evaluated developmental toxicity in animal models are outlined in Table 6-3, listing the fluoride dosing regimens and main observations. High-dose hazard identification studies, such as a recently reported *Xenopus* embryo development study using the FETAX assay (Goh and Neff 2003), suggest that developmental events are susceptible to disruption by fluoride.

For risk evaluation, several comprehensive studies of fluoride effects on development using standard guidelines and adequate numbers of animals have been conducted in rats and rabbits (Collins et al. 1995; Heindel et al. 1996; Collins et al. 2001b). Those high-quality studies evaluated fluoride concentrations in drinking water of 0-300 mg/L in rats and 0-400 mg/L in rabbits. Across the studies, there was a trend toward lower maternal body weights and lower maternal intake of food and water at the higher concentrations in both rats and rabbits (250-400 mg/L). Overall, developmental effects of fluoride were minimal, with 250 mg/L in rats being the lowest-observed-adverse-effect level due to skeletal variations (Collins et al. 1995, 2001b). For rabbits, the no-observed-adverse-effect level was >400 mg/L for administration during gestation days 6-19, the period of organogenesis (Heindel et al. 1996).

Human Studies

The few studies gleaned from a search of the literature since 1990 that evaluated developmental effects of fluoride ingestion in humans are outlined in Table 6-4, listing the type of study, estimated fluoride exposure, and main observations. These studies have focused on examining an association between fluoride and three different human developmental outcomes—spina bifida occulta, sudden infant death syndrome, and Down’s syndrome. Two small studies have raised the possibility of an increased incidence of spina bifida occulta in fluorosis-prone areas in India (Gupta et al. 1994, 1995); larger, well-controlled studies are needed to evaluate that possibility further. Studies from New Zealand (Mitchell et al. 1991; Dick et al. 1999) found no association between fluoride and sudden infant death syndrome. In one of those studies (Dick et al. 1999), a nationwide case-control database of sudden infant death syndrome was evaluated for fluoride exposure status and controlled for the method of infant feeding (breast or reconstituted formula) with the conclusion that exposure to fluoridated water prenatally or postnatally at the time of death did not affect the relative risk of sudden infant death syndrome.

A small number of ecologic studies have examined Down’s syndrome (trisomy 21) prevalence among populations in municipalities with differ-
ences in water fluoride concentrations. The possible association of cytogenetic effects with fluoride exposure (see Chapter 10) suggests that Down’s syndrome is a biologically plausible outcome of exposure. There are other indications in the literature that environmental exposures could contribute to an increased incidence of Down’s syndrome births among younger mothers (Read 1982; Yang et al. 1999; Hassold and Sherman 2000; Peterson and Mikkelsen 2000). There are many difficulties with analyzing the available data on Down’s syndrome and fluoride. First, the source of the data on Down’s syndrome births must be considered. Sources have included birth certificates, hospital records, and reports from parents. Birth certificates are not an ideal source of data because signs of Down’s syndrome are not always readily apparent at birth and the condition, even when diagnosed early, is not always recorded on the birth certificate. Thus, considerable differences can be expected in the data collected when different sources are used to determine the incidence of the disorder. At the present time, the only firm diagnosis of Down’s syndrome comes from examination of chromosomes or DNA. Second, the mother’s history of exposure to fluoride is difficult to determine. The fact that a woman has a baby in one city does not mean she is from that city or indicate how long she has been in the region. Third, the age of the mother is an important risk factor in the occurrence of children with Down’s syndrome; the rates rise exponentially with age.

Some fraction of maternal recombination events, prior to the first meiotic division, apparently result in a chromosome 21 tetrad (paired chromosomes each with two chromatids) that is more susceptible to nondisjunction, due to lack of a cross-over or to very proximal or very distal location of the cross-over (Lamb et al. 1996; 1997; Brown et al. 2000; Hassold and Sherman 2000; Petersen and Mikkelsen 2000; Pellestor et al. 2003). Production of the susceptible tetrad occurs during the mother’s own fetal development and appears to be age-independent (Lamb et al. 1996; 1997; Brown et al. 2000; Hassold and Sherman 2000; Hassold et al. 2000; Petersen and Mikkelsen 2000). However, the likelihood that the susceptible tetrad will be processed abnormally—i.e., will give rise to nondisjunction rather than segregating normally—appears to be age-dependent, with an increased likelihood of nondisjunction with increased maternal age (Lamb et al. 1996; 1997; Brown et al. 2000; Hassold and Sherman 2000; Hassold et al. 2000; Wolstenholme and Angell 2000; Petersen and Mikkelsen 2000). This age-related effect involves a disturbance of the meiotic process (e.g., failure of the spindle apparatus or degradation of a meiotic protein), inhibition of a DNA repair enzyme, or an environmental exposure (Lamb et al. 1997; Brown et al. 2000; Hassold and Sherman 2000; Petersen and Mikkelsen 2000; Wolstenholme and Angell 2000; Pellestor et al. 2003), and is probably multifactorial (Pellestor et al. 2003). Environmental factors that disrupt the meiotic process could increase the likelihood of Down syndrome births in younger mothers, essentially increasing the likelihood of incorrect segregation of susceptible tetrads to that generally seen in older women. According to Petersen and Mikkelsen (2000), “the findings suggest that aging alone is sufficient to disrupt the meiotic process, whereas in younger women there is a higher requirement for a genetic or environmental factor for nondisjunction to occur.” For example, Yang et al. (1999) reported that for a specific type of maternal meiotic error, for younger mothers, there was a significant association with environmental exposures (in this case, maternal smoking, especially in combination with the use of oral contraceptives) around the time of conception.
### TABLE 6-3 Developmental Toxicity Studies

<table>
<thead>
<tr>
<th>Species, Sex, Number</th>
<th>Exposure Route</th>
<th>Concentration/ Dose</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, F, 33-35/group</td>
<td>Drinking water</td>
<td>0, 10, 25, 100, 175, 250 mg/L (NaF) Mean doses: 0, 1.4, 3.9, 15.6, 24.7, and 25.1 mg/kg/day (NaF)</td>
<td>From day of sperm detection to gestation day 20</td>
</tr>
<tr>
<td>Rat, F, 10/group</td>
<td>Drinking water</td>
<td>40 mg/kg/day (NaF)</td>
<td>From day 6 to 19 of gestation</td>
</tr>
<tr>
<td>Rat, M, F, 40-50 animals/group from 4 or 5 litters at each age</td>
<td>Intraperitoneal injection</td>
<td>0, 30 and 48 mg/kg (NaF)</td>
<td>Single injection on postnatal day 1, 8, 15, or 29</td>
</tr>
<tr>
<td>Rat, M, F, 26/group Rabbit, M, F, 26/group</td>
<td>Drinking water</td>
<td>Rat: 0, 50, 150, 300 mg/L (NaF) (mean doses 6.6, 18.3, and 27.1 mg/kg/day) Rabbit: 0, 100, 200, 400 mg/L (NaF) (mean doses 10.3, 18.1, and 29.2 mg/kg/day)</td>
<td>Rat: from gestational day 6 to 15 Rabbit: from gestational day 6 to 19</td>
</tr>
<tr>
<td>Rat, M, F, 3 generations (F0, F1, F2), F0: 48 M, 48 F/group; F1: 36 M, 36 F/group; F2: 238 fetuses</td>
<td>Drinking water</td>
<td>0, 25, 100, 175, 250 mg/L (NaF) Mean doses: (F0): 3.4, 12.4, 18.8, 28.0 mg/kg/day (NaF) (F1): 3.4, 13.2, 19.3, 25.8 mg/kg/day (NaF)</td>
<td>F0: 10 weeks</td>
</tr>
<tr>
<td>Frog (Xenopus) embryo, 20/group</td>
<td>Incubated with NaF solution</td>
<td>100-1,000 ppm (NaF)</td>
<td>2, 3, 4, 5, 9, 14.75 hours after fertilization</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** EC50, median effective concentration; F, female; LC50, median lethal concentration; M, male; NOAEL, no-observed-adverse-effect level.
<table>
<thead>
<tr>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant reductions in maternal water consumption in the two highest-dose groups and a significant reduction in maternal feed consumption in the high-dose group. Body weights of dams were reduced in the higher-dose groups. The only significant developmental effect was an increase in the average number of fetuses with three or more skeletal variations in the 25.1-mg/kg/day group.</td>
<td>Collins et al. 1995</td>
</tr>
<tr>
<td>NaF caused significantly lowered body weight, feed consumption, absolute uterine weight, and number of implantations. Higher incidence of skeletal (14th rib, dumbbell-shaped 5th sternebrae, incomplete ossification of skull, wavy ribs) and visceral abnormalities (subcutaneous hemorrhage) in fetuses. Vitamin D treatment improved reductions in body weight, feed consumption, and uterine weight.</td>
<td>Guna and Verma 2001</td>
</tr>
<tr>
<td>Changes in renal function included decreased body weight after NaF treatment at 30 or 48 mg/kg; increased kidney/body weight ratio in the 48-mg/kg group; decreased urinary pH; decreased chloride excretion in the 48 mg/kg group, and increased urinary volume 120 hours after treatment. Renal toxicity was observed in postweaning day 29 rats. NaF exposure resulted in increased kidney/body weight ratio and kidney weight, profound diuresis, decreased urinary osmolality, and decreased ability to concentrate urine during water deprivation. Decrease in urinary chloride excretion was observed for the first 2 days after exposure; it was increased in water-deprived rats 120 hours after treatment. Hematuria and glucosuria were observed for 2 days after treatment with 48 mg/kg. Renal sensitivity noted after weaning in day 29 rats. Histological lesions noted in proximal tubules of treated day 29 rats.</td>
<td>Datson et al. 1985</td>
</tr>
<tr>
<td>In high-dose group, initial decreased body weight gain (recovered over time) and decreased water consumption. No clinical signs of toxicity were observed. In both the rabbit and rat, maternal exposure to NaF during organogenesis did not substantially affect frequency of postimplantation loss, mean fetal body weight/litter, and visceral or skeletal malformations. The NOAEL for maternal toxicity was 18 mg/kg/day (NaF) in drinking water for rats and rabbits. The NOAEL for developmental toxicity was greater than 27 mg/kg/day (NaF) for rats and greater than 29 mg/kg/day for rabbits.</td>
<td>Heindel et al. 1996</td>
</tr>
<tr>
<td>No dose-related feed consumption or mean body weight gain in either F₀ or F₁ females. Statistically significant decreases in fluid consumption for F₀ at 250 mg/L and F₁ at 175 and 250 mg/L. Corpora lutea, implants, fetal morphological development, and viable fetuses were similar in all groups. No dose-related anomalies in internal organs were observed in F₂ fetuses. Ossification of the hyoid bone was significantly decreased among F₂ fetuses at 250 mg/L.</td>
<td>Collins et al. 2001b</td>
</tr>
<tr>
<td>Reduction in head-tail lengths and dysfunction of the neuromuscular system of the tadpoles. EC₅₀ for malformation in growth after exposure to NaF 5 hours after fertilization is 184 ppm. Calculated LC5₀ is 632 ppm. Values for EC₅₀ and LC₅₀ met the limits established for a teratogen in frog embryos.</td>
<td>Goh and Neff 2003</td>
</tr>
<tr>
<td>Subjects</td>
<td>Exposure Route, Duration</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Pregnant women (mean age 29; n = 91), routine examination at 6th month of pregnancy, 4 groups</td>
<td>Oral doses, taken during final trimester of pregnancy</td>
</tr>
<tr>
<td>Pregnant women (n = 25)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Children (ages 4-12; n = 30)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Pregnant women (n = 22)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Subjects</td>
<td>Exposure</td>
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<tr>
<td>Pregnant women (mean age 29; n = 91), routine examination at 6th month of pregnancy, 4 groups</td>
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<td>Children (ages 4-12; n = 30)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Pregnant women (n = 22)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Fetuses (14-36 weeks of intrauterine life; n = 64)</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Children from India (ages 5-12; n = 50) with dental and/or skeletal fluorosis</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Data for mothers under age 30, Down’s syndrome birth rates in five counties of metropolitan Atlanta, Georgia (reanalysis of Erickson 1976)</td>
<td>Drinking water</td>
</tr>
</tbody>
</table>

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Table 6-4: Human Developmental Studies
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Exposure Route, Duration</th>
<th>Concentration/Dose</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from literature search on studies of Down’s syndrome and exposure to fluoride</td>
<td>Drinking water</td>
<td>Range from all studies was 0-2.8 mg/L</td>
<td>Six ecological studies were included in the evaluation. Crude relative risk ranged from 0.84 to 3.0. Four studies found no significant association between Down’s syndrome and water fluoride concentration. Two studies showed increased incidence of Down’s syndrome with increased water fluoride concentrations ($P &lt; 0.05$). All the studies scored poorly on the validity assessment. Only two studies controlled for confounding factors, only one of which presented summary outcome measures.</td>
<td>Whiting et al. 2001</td>
</tr>
<tr>
<td>Data from literature search on SIDS mortality rate for 1980-1984 in New Zealand</td>
<td>Drinking water</td>
<td>Median fluoridation was ≤1 g/m^3</td>
<td>Strong negative correlation between SIDS and mean daily temperature of -0.83 ($P = 0.0001$). Nonsignificant correlation between SIDS and average fluoridation ($P = 0.24$). Mean daily temperature was significant while average fluoridation was not. Daily temperature was a significant predictor of SIDS after removing average fluoridation from the model.</td>
<td>Mitchell et al. 1991</td>
</tr>
<tr>
<td>485 postneonatal deaths attributed to SIDS; 1,800 control infants</td>
<td>Drinking water</td>
<td>0.7-1.0 mg/L (artificial) 0.1-0.3 mg/L (natural)</td>
<td>Exposed infants to fluoridated water in utero were not at increased risk for SIDS, adjusted odds ratio 1.19. Fluoridated water was not associated with increased risk for SIDS among breastfed infants. Fluoridated formula feeding, compared with unfluoridated formula, showed no increase of SIDS. No interaction between fluoridation and infant feeding.</td>
<td>Dick et al. 1999</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** SIDS, sudden infant death syndrome.
Two early papers (Rapaport 1956, 1963) reported an association between elevated rates of Down’s syndrome and high water fluoride concentrations. Rapaport also was the first to suggest that maternal age might be an important consideration, with the association between drinking water fluoride concentrations and elevated rates of Down’s syndrome particularly pronounced among young mothers. However, the impact of Rapaport’s observations is limited by some significant methodological concerns, including the use of crude rates as opposed to maternal age-specific rates, limited case ascertainment, and the presentation of crude rates per 100,000 population as opposed to per live births. Several subsequent reports (Berry 1958; Needleman et al. 1974; Erickson et al. 1976; Erickson 1980) studied the association of Down’s syndrome with fluoride or water fluoridation. Berry (1958) found little difference in rates of Down’s syndrome between communities with relatively high and low water fluoride concentrations; however, the populations evaluated were small, and maternal age was not considered in the analysis. Needleman et al. (1974) found a positive association between water fluoride concentration and Down’s syndrome incidence when crude incidence rates were compared; however, this apparent association was largely lost when the comparison was limited to before and after fluoridation for a subset of towns that introduced water fluoridation, an attempt to partially control for maternal age. Erickson et al. (1976) used data from two sources, the Metropolitan Atlanta Congenital Malformations Surveillance Program and the National Cleft Lip and Palate Intelligence Service. The metropolitan Atlanta database is particularly robust, with detailed retrospective ascertainment. Erickson et al. (1976) found no overall association between the crude incidence rates of Down’s syndrome and water fluoridation; however, their data suggested a possible increased rate of Down’s syndrome among births to mothers below age 30. Takahashi (1998) grouped Erickson’s metropolitan Atlanta data for mothers under 30 and calculated a highly significant association ($P < 0.005$) between fluoridated water and Down’s syndrome births to young mothers. A recent review (Whiting et al. 2001) has evaluated the quality of the literature and concluded that an association between water fluoride concentration and Down’s syndrome incidence is inconclusive. While the committee agrees with this overall characterization, the review by Whiting et al. was problematic. For example, it described all six studies as ecological and all but one (Rapaport 1956) as having found the majority of cases. However, some studies were partially ecologic, assigning exposure at the group level but categorizing case status and limited covariates (age, race) at the individual level. Erickson (1980) ascertained cases via birth certificates and explicitly acknowledged problems with this approach.

Overall, the available studies of fluoride effects on human development
are few and have some significant shortcomings in design and power, limiting their impact.

FINDINGS

A large number of reproductive and developmental studies in animals have been conducted and published since 1990, and the overall quality of the database has improved significantly. High-quality studies in laboratory animals over a range of fluoride concentrations (0-250 mg/L in drinking water) indicate that adverse reproductive and developmental outcomes occur only at very high concentrations. A few studies of human populations have suggested that fluoride might be associated with alterations in reproductive hormones, fertility, and Down’s syndrome, but their design limitations make them of little value for risk evaluation.

RECOMMENDATIONS

- Studies in occupational settings are often useful in identifying target organs that might be susceptible to disruption and in need of further evaluation at the lower concentrations of exposure experienced by the general population. Therefore, carefully controlled studies of occupational exposure to fluoride and reproductive parameters are needed to further evaluate the possible association between fluoride and alterations in reproductive hormones reported by Ortiz-Perez et al. (2003).

- Freni (1994) found an association between high fluoride concentrations (3 mg/L or more) in drinking water and decreased total fertility rate. The overall study approach used by Freni has merit and could yield valuable new information if more attention is given to controlling for reproductive variables at the individual and group levels. Because that study had design limitations, additional research is needed to substantiate whether an association exists.

- A reanalysis of data on Down’s syndrome and fluoride by Takahashi (1998) suggested a possible association in children born to young mothers. A case-control study of the incidence of Down’s syndrome in young women and fluoride exposure would be useful for addressing that issue. However, it may be particularly difficult to study the incidence of Down’s syndrome today given increased fetal genetic testing and concerns with confidentiality.
Neurotoxicity and Neurobehavioral Effects

This chapter evaluates the effects of fluoride on the nervous system and behavior, with particular emphasis on studies conducted since the earlier NRC (1993) review. The human data include epidemiologic studies of populations exposed to different concentrations of fluoride and individual case studies. In addition, laboratory studies of behavioral, biochemical, and neuroanatomical changes induced by fluoride have been reviewed and summarized. At the end of the chapter, conclusions and recommendations for future research are presented.

HUMAN STUDIES

Cognitive Effects

Several studies from China have reported the effects of fluoride in drinking water on cognitive capacities (X. Li et al. 1995; Zhao et al. 1996; Lu et al. 2000; Xiang et al. 2003a,b). Among the studies, the one by Xiang et al. (2003a) had the strongest design. This study compared the intelligence of 512 children (ages 8-13) living in two villages with different fluoride concentrations in the water. The IQ test was administered in a double-blind manner. The high-fluoride area (Wamiao) had a mean water concentration of 2.47 ± 0.79 mg/L (range 0.57-4.50 milligrams per liter [mg/L]), and the low-fluoride area (Xinhua) had a mean water concentration of 0.36 ± 0.15 mg/L (range 0.18-0.76 mg/L). The populations studied had comparable iodine and creatinine concentrations, family incomes, family educational levels, and other factors. The populations were not exposed to other sig-
significant sources of fluoride, such as smoke from coal fires, industrial pollution, or consumption of brick tea. Thus, the difference in fluoride exposure was attributed to the amount in the drinking water. Mean urinary fluoride concentrations were found to be $3.47 \pm 1.95$ mg/L in Wamiao and $1.11 \pm 0.39$ mg/L in Xinhuai. Using the combined Raven’s Test for Rural China, the average intelligence quotient (IQ) of the children in Wamiao was found to be significantly lower ($92.2 \pm 13.00$; range, 54-126) than that in Xinhuai ($100.41 \pm 13.21$; range, 60-128).

The IQ scores in both males and females declined with increasing fluoride exposure. The distribution of IQ scores from the females in the two villages is shown in Figure 7-1. A comparable illustration of the IQ scores of males is shown in Figure 7-2. The number of children in Wamiao with scores in the higher IQ ranges was less than that in Xinhuai. There were corresponding increases in the number of children in the lower IQ range. Modal scores of the IQ distributions in the two villages were approximately the same. A follow-up study to determine whether the lower IQ scores of the children in Wamiao might be related to differences in lead exposure disclosed no significant difference in blood lead concentrations in the two groups of children (Xiang et al. 2003b).

A study conducted by Lu et al. (2000) in a different area of China also compared the IQs of 118 children (ages 10-12) living in two areas with different fluoride concentrations in the water ($3.15 \pm 0.61$ mg/L in one area and $0.37 \pm 0.04$ mg/L in the other). The children were lifelong residents of the villages and had similar social and educational levels. Urinary fluoride concentrations were measured at $4.99 \pm 2.57$ mg/L in the high-fluoride area and $1.43 \pm 0.64$ mg/L in the low-fluoride area. IQ measurements using the Chinese Combined Raven’s Test, Copyright 2 (see Wang and Qian 1989), showed significantly lower mean IQ scores among children in the high-fluoride area ($92.27 \pm 20.45$) than in children in the low-fluoride area ($103.05 \pm 13.86$). Of special importance, 21.6% of the children in the high-fluoride village scored 70 or below on the IQ scale. For the children in the low-fluoride village, only 3.4% had such low scores. Urinary fluoride concentrations were inversely correlated with mental performance in the IQ test. Qin and Cui (1990) observed similar negative correlation between IQ and fluoride intake through drinking water.

Zhao et al. (1996) also compared the IQs of 160 children (ages 7-14)

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1In the following sections of the chapter, the word “fluoride” is used frequently to indicate what is being measured in blood or urine of people or animals after some treatment with a fluoride. According to medical dictionaries, the word fluoride refers to any binary compound containing fluorine. In many studies, the amount of fluoride reported in urine, blood, or tissue of subjects is the amount of fluorine in the specimen(s). The measurements are frequently referred to as the amount of fluoride present. Furthermore, it is virtually impossible to distinguish between the species of fluoride measured.
lacking in a high-fluoride area (average concentration of 4.12 mg/L) with those of children living in a low-fluoride area (average concentration 0.91 mg/L). Using the Rui Wen Test, the investigators found that the average IQ of children in the high-fluoride area (97.69) was significantly lower than that of children in the low-fluoride area (105.21). No sex differences were found, but, not surprisingly, IQ scores were found to be related to parents’
education. The investigators also reported that enamel fluorosis was present in 86% of the children in the high-exposure group and in 14% of the children in the low-exposure group and that skeletal fluorosis was found only in the high-exposure group at 9%.

Another Chinese study evaluated fluoride exposure due to inhalation of soot and smoke from domestic coal fires used for cooking, heating, and drying grain (Li et al. 1995). Many of the children exhibited moderate to severe enamel fluorosis. The average IQ of 900 children (ages 8-13) from an area with severe enamel fluorosis was 9-15 points lower than the average IQ of children from an area with low or no enamel fluorosis. Urinary fluoride concentrations were found to be inversely correlated with IQ, as measured by the China Rui Wen Scale for Rural Areas, and were monotonically related to the degree of enamel fluorosis. Studies based on fluoride exposure from the inhalation of smoke from coal fires are difficult to interpret because of exposure to many other contaminants in smoke.

The significance of these Chinese studies is uncertain. Most of the papers were brief reports and omitted important procedural details. For example, some studies used a modification of the Raven Progressive Matrix test but did not specify what the modifications were or describe how the test was administered. Most of the studies did not indicate whether the IQ tests were administered in a blinded manner. Some of the effects noted in the studies could have been due to stress induced by the testing conditions. Without detailed information about the testing conditions and the tests themselves, the committee was unable to assess the strength of the studies. Despite this, the consistency of the collective results warrants additional research on the effects of fluoride on intelligence in populations that share similar languages, backgrounds, socioeconomic levels, and other commonalities.

It should be noted that many factors outside of native intelligence influence performance on IQ tests. One factor that might be of relevance to fluoride is impairment of thyroid gland function (see Chapter 8). For example, hypothyroidism produces tiredness, depression, difficulties in concentration, memory impairments, and impaired hearing. In addition, there is some evidence that impaired thyroid function in pregnant women can lead to children with lower IQ scores (Klein et al. 2001).

Mental and Physiological Changes

There are numerous reports of mental and physiological changes after exposure to fluoride from various routes (air, food, and water) and for various time periods (Waldbott et al. 1978). A number of the reports are, in fact, experimental studies of one or more individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under “blind” conditions. In most cases, the symptoms disappeared with the elimi-
nation of exposure to fluoride and returned when exposure was reinstated. In some instances, when the fluoride was given in water, this procedure was repeated several times under conditions in which neither the patient nor the provider of the fluoride knew whether the water contained fluoride. Also reported are instances when fluoride-produced symptoms occurred when people moved into a community with fluoridated water but disappeared when the individuals moved to a nonfluoridated community.

Spittle (1994) reviewed surveys and case reports of individuals exposed occupationally or therapeutically to fluoride and concluded there was suggestive evidence that fluoride could be associated with cerebral impairment. A synopsis of 12 case reports of fluoride-exposed people of all ages showed common sequelae of lethargy, weakness, and impaired ability to concentrate regardless of the route of exposure. In half the cases, memory problems were also reported. Spittle (1994) described several of the biochemical changes in enzymatic systems that could account for some of the psychological changes found in patients. He suggested that behavioral alterations found after excessive exposure could be due to the disruption of the N-H bonds in amines, and subsequently in proteins, by the production of N-F bonds (Emsley et al. 1981). This unnatural bond would distort the structure of a number of proteins with the collective potential to cause important biological effects. Fluorides also distort the structure of cytochrome-c peroxidase (Edwards et al. 1984). Spittle also noted the likelihood of fluoride interfering with the basic cellular energy sources used by the brain through the formation of aluminum fluorides (Jope 1988) and subsequent effects on G proteins.

Effects of Silicofluorides

It has been suggested that the silicofluorides used to fluoridate drinking water behave differently in water than other fluoride salts (see Chapter 2 for further discussion) and produce different biological effects. For example, adding sodium silicofluoride (Na$_2$SiF$_6$) or fluorosilicic acid (H$_2$SiF$_6$) to drinking water has been reported to increase the accumulation of the neurotoxicant lead in the body (Masters and Coplan 1999; Masters et al. 2000). This association was first attributed to increased uptake of lead (from whatever source) caused by fluoride. However, enhanced lead concentrations were found only when the water treatments were made with a fluorosilicate and in children already in a high-lead exposure group.

Urbansky and Schock (undated, 2000) took exception to almost all aspects of the studies by Masters and Coplan on the fluorosilicates. They argued that, under the conditions prevailing at the time of the addition of silicofluorides to drinking water, silicofluorides would be completely hydrolyzed before they reached the consumer’s tap (Urbansky and Schock 2000). Measurement techniques and statistical methods were also questioned. They
concluded that there is no “credible evidence” that water fluoridation has any quantifiable effect on the solubility, bioavailability, or bioaccumulation of any form of lead.

Another issue that has been raised about differential effects of silicofluorides comes from the dissertation of Westendorf (1975). In that study, silicofluorides were found to have greater power to inhibit the synthesis of cholinesterases, including acetylcholinesterase, than sodium fluoride (NaF). For example, under physiological conditions, one molar equivalent of silicofluoride is more potent in inhibiting acetylcholinesterase than six molar equivalents of NaF (Knappwost and Westendorf 1974). This could produce a situation in which acetylcholine (ACh) accumulates in the vicinity of ACh terminals and leads to excessive activation of cholinergic receptors in the central and peripheral nervous system. At high concentrations, agents with this capability are frequently used in insecticides and nerve gases. At intermediate concentrations, choking sensations and blurred vision are often encountered. Modifications of the effectiveness of the acetylcholinergic systems of the nervous system could account for the fact that, even though native intelligence per se may not be altered by chronic ingestion of water with fluoride ranging from 1.2 to 3 mg/L, reaction times and visuospatial abilities can be impaired. These changes would act to reduce the tested IQ scores. Such noncognitive impairments in children were reported in a meeting abstract (Calderon et al. 2000), but a full publication has not been issued. Extended reaction times have been associated with impaired function of the prefrontal lobes, a behavioral change not directly tied to alterations in IQ (Winterer and Goldman 2003). Because almost all IQ tests are “time-restricted,” slow reaction times would impair measured performance.

An interesting set of calculations was made by Urbansky and Schock (undated)—namely, compilation of the binding strengths of various elements with fluorine. They studied eight different complexes. Aluminum and fluorine have the highest binding affinity. Fluorine also forms complexes with other elements including sodium, iron, calcium, magnesium, copper, and hydrogen. Associations with some of these other elements may have implications for some of the neurotoxic effects noted after fluoride or SiF exposure.

Dementia

For more than 30 years it has been known that Alzheimer’s disease is associated with a substantial decline in cerebral metabolism (Sokoloff 1966). This original observation has been replicated many times since then. The decrease is reflected in the brain’s metabolic rate for glucose, cerebral rate for oxygen, and cerebral blood flow. In terms of reduced cerebral blood flow, the reduction found in Alzheimer’s patients is about three times
greater than in patients with multi-infarct dementia. As early as 1983, Foster et al. (1983) demonstrated a general decline in the rate of utilization of glucose with the marker F-2-fluorodeoxyglucose with a positron-emission tomography scan. Recently, over and above the general decline in aerobic metabolism, several patterns of enhanced decreases in energy utilization have been demonstrated. The temporal, parietal, and frontal regions are areas with some of the greatest reductions (Weiner et al. 1993; Starkstein et al. 1995). It is possible that the decline in glucose utilization is an early sign of the onset of dementia (Johnson et al. 1988; Silverman and Small 2002).

In addition there is evidence from a number of sources that alterations induced by Alzheimer’s disease can be observed in many body regions and in blood. This indicates that the disease has system-wide effects in the body. One system particularly sensitive to carbohydrate utilization is the collection of areas involved with the synthesis of ACh. The release of this transmitter is also negatively affected by the interruption of aerobic metabolism and the effect can be noticed in the projection fields of the cholinergic systems.

Fluoride produces additional effects on the ACh systems of the brain by its interference with acetylcholinesterase.

Most of the drugs used today to treat Alzheimer’s disease are agents that enhance the effects of the remaining ACh system. Nevertheless, it must be remembered that one certain characteristic of Alzheimer’s disease is a general reduction of aerobic metabolism in the brain. This results in a reduction in energy available for neuronal and muscular activity.

Because of the great affinity between fluorine and aluminum, it is possible that the greatest impairments of structure and function come about through the actions of charged and uncharged AlF complexes (AlF_x). In the late 1970s and through the early 1990s there was considerable interest in the possibility that elemental aluminum was a major contributing factor to the development of dementia of the Alzheimer’s variety as well as to other neurological disorders. In a study of more than 3,500 French men and women above the age of 65 (Jacqmin et al. 1994), a significant decrease in cognitive abilities was found when their drinking water contained calcium, aluminum, and fluorine. Only aluminum showed any relation to cognitive impairment and that depended on the pH of the drinking water being below 7.3. Curiously, at higher pH values, a favorable effect on cognitive actions was found. In recent work with animals, aluminum-induced behavioral changes similar to those found in human dementia, as well as correlated histological changes in animals’ brains, were found (Miu et al. 2003). Active research continues at the cellular level on the neural mechanisms disturbed by aluminum (Becaria et al. 2003; Millan-Plano et al. 2003). On the epidemiological side there are inconsistencies in the results of different studies. For example, a recent review concludes that “the toxic effects of aluminum cannot be ruled out either, and thus exposure to aluminum should be monitored and
limited as far as possible” (Suay and Ballester 2002). In addition to a depletion of acetylcholinesterase, fluoride produces alterations in phospholipid metabolism and/or reductions in the biological energy available for normal brain functions (see section later in this chapter on neurochemical effects). In addition, the possibility exists that chronic exposure to AlF$_x$ can produce aluminum inclusions with blood vessels as well as in their intima and adventitia. The aluminum deposits inside the vessels and those attached to the intima could cause turbulence in the blood flow and reduced transfer of glucose and O$_2$ to the intercellular fluids. Finally histopathological changes similar to those traditionally associated with Alzheimer’s disease in people have been seen in rats chronically exposed to AlF (Varner et al. 1998).

ANIMAL STUDIES

Behavioral Changes

Studies of NaF

One of the most frequently cited and much discussed studies reporting a link between fluoride and behavior is by Mullenix et al. (1995). The study involved administering NaF to rats at different ages. Two groups of rats were exposed to NaF during gestation by subcutaneous injections given to pregnant dams. Other groups of rats received NaF in water beginning at weaning. Another set of rats was exposed to NaF in water in adulthood. Because of differences in the treatment regimes, procedures involved with the transport of animals at different ages, and other alterations in methods between the age groups, the data from the study are meaningful only if they are considered separately.

In “experiment 1,” pregnant dams were subcutaneously injected with NaF at 0.13 mg/kg either on gestational days 14-18 (one or two injections per day, for a total of nine injections) or on days 17-19 (three injections per day). In “experiment 2,” NaF at 75, 100, 125, or 175 mg/L was administered in the drinking water to rats at 21 days of age for 6-20 weeks. In “experiment 3,” 12-week-old rats were given NaF at 100 mg/L in drinking water for 5-6 weeks. Behavioral tests were performed on prenatally treated and weanling rats at 9 weeks of age, and adult-treated rats were tested at the end of their exposure period. Concentrations of fluoride in plasma in seven brain regions were measured at the time of sacrifice.

To appreciate the data generated by the testing procedures, some details of the testing methods and data analysis used in the Mullenix et al. study must be considered. The methods used were ones developed earlier to quantify animal behavior by using computer-based methods (Kernan et al. 1987, 1988; Kernan and Mullenix 1991). The basic procedures involved
the following: The animals were tested in pairs consisting of a treated and a control rat. They were placed in a Plexiglas chamber divided in the middle by a Plexiglas wall to make two adjacent testing chambers. This wall had several holes in it. Thus, each rat could see, hear, and smell its pair-mate. The actual floor space available to each animal was approximately 10 in by 10 in. The chamber was an unusual trapezoidal design with the walls slanting outward from the floor. This shape was created to enhance the clarity of images of the rats recorded by two video cameras. One camera was placed above the testing chambers and another was off to one side. Both were aligned so as to encompass the testing areas of both animals. Sprague-Dawley albino rats were used in the experiments and, to further enhance the pictures, the side away from the horizontally placed camera was black. The floor was also black.

The two video cameras recorded the behavior of both animals simultaneously. The cameras were programmed to take still photos of the animals every second for the 15-minute testing period. Thus, the cameras sent 900 pictures of each animal during a single test period. The computer was programmed to detect five bodily positions, eight “modifiers” (apparently this term means an action with a presumptive goal), and several combinations of postures and modifiers. In all, the computer could record more than 100 combinations of positions, modifiers, and combinations of one or more of the measures indicating the “presumed intentions” of the animals (e.g., groom/attention). For each of these postures or actions or combinations, the number of times it was initiated, the total time spent doing it, and the distribution of the act throughout the 15-minute period were calculated separately for each rat.

In experiment 1, none of the rats treated on gestational days 14-18 showed any behavioral differences from controls. However, among rats treated on gestation days 17-19, male rats were reported to be more active than controls. The increase in activity was attributed to increased instances of grooming and head turning and not enhanced locomotor movement. Plasma concentrations of fluoride were comparable to those of the controls. Fluoride concentrations in the brain were not measured in this group.

In experiment 2, high mortality was observed in the highest treatment group (175 mg/L), and testing was discontinued at that concentration. Female rats exposed to NaF at 125 mg/L had fewer instances of sitting, spent less time sitting, had fewer head turns, and had fewer clusters of grooming bouts than controls. They also showed a reduction in the groom/attention composite index. Females exposed to fluoride in drinking water at 100 mg/L for 6 weeks showed behavioral changes related to grooming, including reduced grooming bouts, reductions in persistent grooming periods, and the grooming/attention cluster. However, these effects were not seen among the females treated for longer periods (20 weeks). Among male rats, changes
in behavior were observed only in the 125 mg/L group evaluated after 16 weeks of treatment. Changes included less sitting, less head turning, more standing, and reductions in grooming behavior. Standing and seeming attention postures were increased in these weanling-exposed rats. Measurements of fluoride in plasma showed an increase in concentration after 6 weeks of exposure to NaF at 100 mg/L in male and female rats. All seven areas of the brain analyzed showed increased concentrations of fluoride. As noted in Chapter 3, the accuracy of these measurements has been questioned (Whitford 1996), because other studies have shown that brain fluoride concentrations are considerably lower than, but proportionate to, those in plasma (Carlson et al. 1960; Whitford et al. 1979).

The computer program used in the behavior analyses also generated a statistic named “RS” that combines all the detected alterations in every recognized mode or modified mode of behavior. This overall index of change was reported as significant in females 6 weeks after the start of NaF treatment at concentrations of 100 and 125 mg/L. The statistic was not changed in males treated with NaF at a concentration of 125 mg/L for 11 weeks.

In experiment 3, only female rats showed behavioral changes compared with controls. Changes included reductions in sitting and grooming. Plasma fluoride concentrations were increased in males and females. Testing of fluoride concentrations in the brain found increased concentrations in the medulla of both sexes and in the hippocampal region of females. As noted above, the accuracy of these measurements has been questioned.

The results from these three experiments are difficult to interpret. One difficulty is interpreting the computer-derived categorization of activity patterns compared with behavioral descriptions commonly used by most animal researchers. For example, increased activity usually refers to increased locomotor activity measured in relatively large open fields or mazes. In the Mullenix et al. study, increased activity is characterized by head turning, grooming behaviors, and sniffing and exploration of the corners of the box, which traditionally are not characterized as part of locomotor activity. The small chambers in which the animals were tested would have prevented much locomotor movement at all.

Another aspect of the study that is a modifying issue is the stress-related experience of the rats before the experiments began. The transportation and associated handling of animals over long distances are known stressors to rats and mice. For experiment 1, the pregnant rats were shipped on day 6 of gestation and were housed singly thereafter. The rats used in experiment 2 were shipped to the laboratory at 17 days of age, along with their dams. The adult rats of experiment 3 were shipped at 10 weeks of age. Because the animals were from the Charles River Laboratories in Kingston, New York, the means of transportation to the laboratory in Boston was likely by truck. The transportation of animals by land or air has been shown to
produce lasting effects on rodents (Isaacson et al. 2003). The histological effects of transportation and relocation include neuronal losses and substantial instances of shrunken or bloated cells, including some with condensed cytoplasmic inclusions. Other signs of stress and neural insult can be seen, including the presence of reactive microglia throughout the brain. These changes might well interact with later fluoride treatments. In essence, this means comparisons between groups can be legitimately made within the several experiments but not between them. Mullenix et al. (1995) interpreted their behavioral results to imply the interruption of hippocampal dysfunction. Another plausible interpretation is that the behavioral change might have involved alterations in the adrenal-pituitary axis (Gispen and Isaacson 1986).

The results of the Mullenix studies are difficult to compare with studies from other laboratories. The apparatus used has a unique configuration, the chambers were small, and the paired animals were in visual, olfactory, and auditory contact with each other. The data generated are largely derived in idiosyncratic ways by the hardware and software of a relatively complex computer program. From a practical standpoint, it would be extremely difficult for other investigators to replicate the study. The committee is aware there has been debate about the interpretation and significance of the findings of this study. For example, Ross and Daston (1995) note that decreased grooming can be an indication of illness. Because of the high concentrations of fluoride used in the study, it is possible that the animals had gastrointestinal or renal disturbances (Whitford and Taves 1973; Pashley et al. 1984; also see Chapter 9). As discussed above, the committee agrees there are difficulties with interpreting the results of the study, but those difficulties do not warrant dismissal of the results. The study provided some evidence that exposure to fluoride (prenatal, weaning, or in adulthood) might have affected the behavior of rats, albeit almost always in a gender-specific fashion.

In a different type of study, Swiss albino mice were treated with NaF at 30, 60, and 120-mg/L in water for 30 days and behavioral tests were performed daily 1 hour after treatment. The testing included akinesia, catalepsy, swim endurance, and simple maze tests. Animals in the 120 mg/L group scored more poorly in all the tests. Histological changes observed in the brains of these animals are discussed later in this chapter (Bhatnagar et al. 2002).

Paul et al. (1998) investigated the effects of NaF on the motor activity and coordination of female Wistar rats. The rats were treated with NaF at 20 or 40 mg/kg/day by gastric intubation for 2 months and were tested in an activity chamber and on a rota-rod apparatus. Only female rats were used because of the high mortality rates among males in preliminary studies. In both treatment groups, food intake and body weight gain were reduced in
a dose-dependent manner. A reduction in spontaneous motor activity was based on results from an apparatus that recorded every type of movement, bodily adjustment, or twitch. This should not be confused with increased activity as measured by locomotor movements in a large arena. In the rotarod motor coordination test, no significant changes were observed between the treated and control rats. There was a dose-related decrease in cholinesterase in the blood but not in the brain. Similar effects on motor activity have been observed in other studies in which rats were treated with NaF at 500 mg/L in drinking water. Alterations of acetylcholinesterase concentrations were found in the brain at this concentration (Ekambaram and Paul 2001, 2002).

Studies of AlF$_3$

Varner et al. (1994) studied the effects of chronic administration of aluminum fluoride (AlF$_3$), on the behavior of Long-Evans rats. AlF$_3$ was administered in drinking water at concentrations of 0.5, 5.0, or 50 mg/L. In terms of fluorine, these values translate into the equivalent of 0.34, 3.4, and 34 mg/L. The animals were between 130 and 154 days old at the beginning of the experiment and were maintained on this program for 45 weeks. In the animals treated with AlF$_3$ at 5 and 50 mg/L, no differences in behavior were found in activity in an open field, in patterns of stride when walking, in spontaneous alternation of arms in a T-maze, in a motor coordination test, or in two tests of learning and memory in the Morris water maze. (Rats in the 0.5-mg/L group were too few to provide meaningful results.) The only behavioral change noted was a lack of preference of the location of a banana odor over the location of a lemon odor. Control animals generally prefer the banana odor. This overall lack of behavioral effects occurred in spite of extensive histological changes associated with neuronal damage and cell death in the hippocampus and other parts of the forebrain.

Anatomy

The complete analyses of the changes found in the brains of rats given one of the three doses of AlF$_3$ used by Varner et al. (1994) were reported in a separate paper (Varner et al. 1993). All groups of the AlF$_3$-exposed rats had significant losses of cells in the CA1 and CA3 areas of the hippocampus, but the losses were not dose dependent. Two types of cellular anomalies were found in the treated animals: (1) argentophilic cells throughout the hippocampus and dentate gyrus with considerable sparing of cells in the CA2 region; and (2) increased aluminum fluorescence in most of the brain, especially in the inner and outer linings of a large number of blood vessels, both large and small. Intravascular inclusions of aluminum particles were
sometimes noted within blood vessels. Cells containing aluminum inclusions were not uncommon. This enhancement of aluminum deposits is not surprising because the amount of aluminum found in the brain was almost double that found in control animals.

Varner et al (1998) undertook a second study to determine the relative contribution of fluoride to the high mortality found in the 0.5-mg/L group of the earlier study, to extend the histological procedures used to evaluate the brains, and to determine whether the high death rates after this low dose would be found on replication. Three groups of nine adult rats were administered AlF$_3$ at 0.5 mg/L, NaF at 2.1 mg/L (containing the same amount of fluoride as the AlF$_3$ group), or double-distilled deionized water for 1 year. During that time six of nine animals drinking the AlF$_3$ water died, three of the nine animals drinking the NaF died, and one animal from the control group died. Aluminum content in brain, kidney, and liver was measured by a direct current plasma technique modified for use with tissues containing substantial fat. Brains from both the NaF and the AlF$_3$ groups had more than twice as much aluminum as the brains of the control animals. This supports the work of Strunecka et al. (2002) indicating that fluoride enhances the uptake of aluminum. But, the uptake was organ specific. There was no increase of aluminum found in the kidneys or liver. Sections from the brains of all animals were processed in a manner that allowed their staining with hematoxylin and eosin, the Morin stain for aluminum (and counterstained with cresyl violet), and a modified Bielschowsky silver stain as well as with antisera specific for IgM, β-amyloid, or amyloid A.

There was a progressive decline in the appearance of the AlF$_3$ treated rats compared with the NaF or control animals before their demise. Their hair was sparse and their skin had a copper color. Toenails and teeth indicated a condition reflecting a hypermelanosis. Body weights, however, did not vary among the groups. Hemispheric differences in the brain were found in the distribution of aluminum using the Morin staining ultraviolet microscopic procedure. A greater amount of aluminum fluorescence was seen in layers 5 and 6 of the parietal neocortex and hippocampus of the left relative to the right hemisphere in the AlF$_3$-treated rats. Areas CA3 and CA4 were the most affected regions of the hippocampus.

The occurrence of abnormal cells was also determined for all brains. Signs of neuronal anomalies included chromatin clumping, enhanced protein staining, pyknosis, vacuolation, ghost-like swollen appearances of cells, and enhanced silver staining in cell bodies and their processes. Both NaF and AlF$_3$ treatments produced cellular distortions in cortical layers 2 and 3 of both hemispheres, but enhanced cellular abnormalities in layers 5 and 6 were found only in the left hemisphere. Both treatments also produced a diminished number of cells in the left CA3 region of the hippocampus but only the AlF$_3$ treatment reduced cell numbers in this region of the left hemisphere.
hemisphere. These observations are similar to previous findings reported in the brains of cats after intracerebroventricular administration of aluminum chloride (Crapper and Dalton 1973).

Both the AlF$_3$ and the NaF treatments increased staining of neurons for IgM in the right hemisphere. No differences were found among the groups in the presence of IgM on the left side of the brain. Minor amounts of IgM were found in the hippocampus and dentate gyrus but without any group differences. The control group had few instances of β-amyloid but the brains of the AlF$_3$-treated animals demonstrated a bimodal distribution of deposits in the vasculature of the dorsal thalamus. Staining was either very high or nonexistent. The NaF-treated group showed a similar bimodality of accumulation of β-amyloid in the right lateral posterior thalamic region.

The pattern of neuronal degeneration found by Varner et al. (1998) was also found in two other studies (Bhatnager et al. 2002; Shivarajashankara et al. 2002). In the study by Bhatnagar et al. (2002) described earlier in this chapter, the investigators observed a significant number of degenerated nerve cell bodies in hippocampal subregions CA3 and CA4 and in the dentate gyrus. Shivarajashankara et al. (2002) exposed Wistar rats to NaF in utero during the last week of gestation and for 10 weeks after birth. Animals received either 30 or 100 mg/L in their drinking water. At the end of the 10 weeks the animals were sacrificed and their brains were sectioned and stained with cresyl violet. Little change was seen in the 30-mg/L treated animals but the brains of the 100-mg/L treated animals showed large amounts of neurodegeneration. There were only a few normal appearing pyramidal cells in regions CA1 and CA3 of the hippocampus. Almost all the cells in these areas were pyknotic and showed intensely stained protein in their shrunken cytoplasm. Neuronal degeneration, but to a lesser degree, was found in the upper layers of neocortex, the amygdala, and the cerebellum. These areas were not extensively studied by Varner et al. (1998).

The interactions between fluoride and aluminum have been studied in laboratories and in the environment. There is evidence that fluoride enhances the uptake of aluminum and that aluminum reduces the uptake of fluoride (Spencer et al. 1980, Ahn et al. 1995). This complicates predicting the effect of exposure to aluminum- or fluorine-containing complexes in natural situations.

**NEUROCHEMICAL EFFECTS AND MECHANISMS**

A number of studies have examined biochemical changes in the brain associated with fluoride. For example, Guan et al. (1998) reported alterations in the phospholipid content of the brain of rats exposed to NaF at 30 or 100 mg/L for 3-7 months. The most prominent changes were found in phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine.
After 7 months of treatment, ubiquinone was clearly elevated, likely due as a compensatory reaction to the increase in free radicals in the brain. Fluoride has been shown to decrease the activities of superoxide dismutase (Guan et al. 1989) and glutathione peroxidase (Rice-Evans and Hoschstein 1981), the consequences being increased free radicals.

NaF injected subcutaneously into rabbits altered brain lipid metabolism (Shashi 1992b) and concentrations of protein, free amino acid, and RNA in the brain (Shashi et al. 1994).

Using slices of rat neocortex, Jope (1988) found that NaF stimulated the hydrolysis of phosphoinositide by activation of a G protein, Gp. This protein acts as a transducer between receptors and phospholipase C. He also found that a metal chelator added to the preparation eliminated this effect. This information and other observations led to the conclusion that the effective agent in the hydrolysis was an AlF$_x$ complex. Under his experimental conditions, the AlF$_4$ was most likely formed from trace amounts of aluminum derived from the glass or from a fluorine-containing contaminant in a reagent. The addition of increasing amounts of aluminum did not increase the hydrolysis effect. In fact, adding substantial amounts of aluminum inhibited it. As in several types of experiment, it is the low aluminum fluoride concentrations that produce the greatest biochemical or physiological effects. In this regard, it is important to note that, even if aluminum bioavailability is low in rats and in other laboratory species, only a small amount is needed to produce untoward effects (Yokel et al. 2001).

Many of the untoward effects of fluoride are due to the formation of AlF$_x$ complexes. AlF$_x$ and BeF$_x$ complexes are small inorganic molecules that mimic the chemical structure of a phosphate. As such they influence the activity of phosphohydrolases and phospholipase D. Only micromolar concentrations of aluminum are needed to form AlF$_x$ (Sternweis and Gilman 1982). The G protein effects produced by AlF$_x$ are not limited to enzymes that bind phosphates or nucleoside-polyphosphate (Chabre 1990). AlF$_x$ also impairs the polymerization-depolarization cycle of tubulin. This could account for some of the intensely stained neurofilaments in cells in the brains of animals exposed to chronic NaF (Varner et al. 1993, 1998). AlF$_x$ appears to bind to enzyme-bound GDP or ADP, thus imitating GTP or ATP and, in a sense, generating “false messages” within the brain. This binding ability is probably due to the molecular similarities between AlF$_3$(OH) and a phosphate group in the molecular structure, in particular, a tetrahedral arrangement (Strunecka and Patocka 2002).

G protein-coupled receptors mediate the release of many neural transmitters including the catecholamines, serotonin, ACh, and the excitatory amino acids. They also are involved in regulating glucagon, vasopressin, neuropeptides, endogenous opioids, prostaglandins, and other important systemic influences on brain and behavior. AlF$_x$ is also involved in regulating
the pineal melatonin system as well as the thyroid-stimulating hormone-growth hormone connection. It has been said in this regard “every molecule of AlF₆ is the messenger of false information” (Strunecka and Patocka 2002, p. 275). This may be an accurate synopsis of the AlF₆ effect at a single synapse, but the brain is a highly redundant and dispersed communication system containing millions of synapses. Because of this, observable alterations in mental or motor actions might require the formation of a multitude of false messages in a number of brain circuits acting over a prolonged period of time. Thus, the number of false messages required to disrupt an “action pattern” in the brain probably will vary according to the nature of the ongoing activities.

An especially important neurochemical transmitter that reaches almost all areas of the brain is ACh. As discussed above, some studies show that NaF and SiF inhibit cholinesterases, including acetylcholinesterase. The progressive accumulation of ACh at synaptic locations produced by the diminished esterase activity leads to a number of complex effects that can be summarized as an initial increase in stimulation of the target cells but ultimately leads to diminished stimulation—even a blockade of all activity. This earlier dialogue properly emphasized the behavioral importance of cholinergic activity in the brain and body more generally.

Long et al. (2002) reported changes in the number of acetylcholine receptors (nAChRs) in the rat brain due to fluoride. Rats were administered NaF in drinking water at 30 or 100-mg/L for 7 months. Decreased numbers of nAChRα7 subunits were found in the brains of rats from both treatment groups, but only the brains of the 100-mg/L group had diminished nAChRα4 subunits of this receptor. These results are of interest because changes in the nicotinic receptors have been related to the development of Alzheimer’s disease (Lindstrom 1997; Newhouse et al. 1997) and, in frontal brain areas, to schizophrenia (Guan et al. 1999).

**FINDINGS**

**Human Cognitive Abilities**

In assessing the potential health effects of fluoride at 2-4 mg/L, the committee found three studies of human populations exposed at those concentrations in drinking water that were useful for informing its assessment of potential neurologic effects. These studies were conducted in different areas of China, where fluoride concentrations ranged from 2.5 to 4 mg/L. Comparisons were made between the IQs of children from those populations with children exposed to lower concentration of fluoride ranging from 0.4 to 1 mg/L. The studies reported that while modal IQ scores were unchanged, the average IQ scores were lower in the more highly exposed
children. This was due to fewer children in the high IQ range. While the studies lacked sufficient detail for the committee to fully assess their quality and their relevance to U.S. populations, the consistency of the collective results warrant additional research on the effects of fluoride on intelligence. Investigation of other mental and physiological alterations reported in the case study literature, including mental confusion and lethargy, should also be investigated.

Behavioral Effects on Animals

A few animal studies have reported alternations in the behavior of rodents after treatment with fluoride. However, the observed changes were not striking in magnitude and could have been due to alterations in hormonal or peptide activity. Animal studies to date have used conventional methodologies to measure learning and memory abilities or species-typical behaviors in novel locations. The tasks used to measure learning and memory did not require any significant mental effort. No studies were available on higher order mental functions, altered reactions to stress, responses to disease states, or supplemental reactions to known neurotoxins. Procedures are available that could test for cognitive functions, but they are labor intensive and have seldom been used in the past 60 years. One example is the reasoning test designed by Maier (1929), who found that even a small lesion of the neocortex impaired performance on the reasoning test (Maier 1932). A more recent example is the delayed matching to position test with different outcomes (Savage 2001), which have shown that damage to the hippocampus can affect learning.

Fluorosilicates

As noted in Chapter 2, exposure to fluorosilicates could occur under some conditions. There are reports that such chemicals enhance the uptake of lead into the body and brain, whereas NaF does not. Further research is needed to elucidate how fluorosilicates might have different biological effects from fluoride salts.

Neurochemical and Biochemical Changes

Lipids and phospholipids, phosphohydrolases and phospholipase D, and protein content have been shown to be reduced in the brains of laboratory animals subsequent to fluoride exposure. The greatest changes were found in phosphatidylethanolamine, phosphotidylcholine, and phosphotidylserine. Fluorides also inhibit the activity of cholinesterases, including acetylcholinesterase. Recently, the number of receptors for acetylcholine...
has been found to be reduced in regions of the brain thought to be most important for mental stability and for adequate retrieval of memories.

It appears that many of fluoride’s effects, and those of the aluminofluoride complexes are mediated by activation of Gp, a protein of the G family. G proteins mediate the release of many of the best known transmitters of the central nervous system. Not only do fluorides affect transmitter concentrations and functions but also are involved in the regulation of glucagons, prostaglandins, and a number of central nervous system peptides, including vasopressin, endogenous opioids, and other hypothalamic peptides. The AlF$_x$ binds to GDP and ADP altering their ability to form the triphosphate molecule essential for providing energies to cells in the brain. Thus, AlF$_x$ not only provides false messages throughout the nervous system but, at the same time, diminishes the energy essential to brain function.

Fluorides also increase the production of free radicals in the brain through several different biological pathways. These changes have a bearing on the possibility that fluorides act to increase the risk of developing Alzheimer’s disease. Today, the disruption of aerobic metabolism in the brain, a reduction of effectiveness of acetylcholine as a transmitter, and an increase in free radicals are thought to be causative factors for this disease. More research is needed to clarify fluoride’s biochemical effects on the brain.

**Anatomical Changes in the Brain**

Studies of rats exposed to NaF or AlF$_3$ have reported distortion in cells in the outer and inner layers of the neocortex. Neuronal deformations were also found in the hippocampus and to a smaller extent in the amygdala and the cerebellum. Aluminum was detected in neurons and glia, as well as in the lining and in the lumen of blood vessels in the brain and kidney. The substantial enhancement of reactive microglia, the presence of stained intracellular neurofilaments, and the presence of IgM observed in rodents are related to signs of dementia in humans. The magnitude of the changes was large and consistent among the studies. Given this, the committee concludes further research is warranted in this area, similar to that discussed at a February 2-3, 1999, EPA workshop on aluminum complexes and neurotoxicity and that recommended for study by NTP (2002).

**RECOMMENDATIONS**

On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means. To determine the possible adverse effects of fluoride, additional data from both the experimental and the clinical sciences are needed.
• The possibility has been raised by the studies conducted in China that fluoride can lower intellectual abilities. Thus, studies of populations exposed to different concentrations of fluoride in drinking water should include measurements of reasoning ability, problem solving, IQ, and short- and long-term memory. Care should be taken to ensure that proper testing methods are used, that all sources of exposure to fluoride are assessed, and that comparison populations have similar cultures and socioeconomic status.

• Studies of populations exposed to different concentrations of fluoride should be undertaken to evaluate neurochemical changes that may be associated with dementia. Consideration should be given to assessing effects from chronic exposure, effects that might be delayed or occur late-in-life, and individual susceptibility (see Chapters 2 and 3 for discussion of sub-populations that might be more susceptible to the effects of fluoride from exposure and physiologic standpoints, respectively).

• Additional animal studies designed to evaluate reasoning are needed. These studies must be carefully designed to measure cognitive skills beyond rote learning or the acquisition of simple associations, and test environmentally relevant doses of fluoride.

• At the present time, questions about the effects of the many histological, biochemical, and molecular changes caused by fluorides cannot be related to specific alterations in behavior or to known diseases. Additional studies of the relationship of the changes in the brain as they affect the hormonal and neuropeptide status of the body are needed. Such relationships should be studied in greater detail and under different environmental conditions.

• Most of the studies dealing with neural and behavioral responses have tested NaF. It is important to determine whether other forms of fluoride (e.g., silicofluorides) produce the same effects in animal models.
Effects on the Endocrine System

The endocrine system, apart from reproductive aspects, was not considered in detail in recent major reviews of the health effects of fluoride (PHS 1991; NRC 1993; Locker 1999; McDonagh et al. 2000a; WHO 2002; ATSDR 2003). Both the Public Health Service (PHS 1991) and the World Health Organization (WHO 2002) mentioned secondary hyperparathyroidism in connection with discussions of skeletal fluorosis, but neither report examined endocrine effects any further. The Agency for Toxic Substances and Disease Registry (ATSDR 2003) discussed four papers on thyroid effects and two papers on parathyroid effects and concluded that “there are some data to suggest that fluoride does adversely affect some endocrine glands.” McDonagh et al. (2000a) reviewed a number of human studies of fluoride effects, including three that dealt with goiter and one that dealt with age at menarche. The following section reviews material on the effects of fluoride on the endocrine system—in particular, the thyroid (both follicular cells and parafollicular cells), parathyroid, and pineal glands. Each of these sections has its own discussion section. Detailed information about study designs, exposure conditions, and results is provided in Appendix E.

THYROID FOLLICULAR CELLS

The follicular cells of the thyroid gland produce the classic thyroid hormones thyroxine (T4) and triiodothyronine (T3); these hormones modulate a variety of physiological processes, including but not limited to normal growth and development (Larsen et al. 2002; Larsen and Davies 2002; Goodman 2003). Between 4% and 5% of the U.S. population may be af-
fected by deranged thyroid function (Goodman 2003), making it among the most prevalent of endocrine diseases (Larsen et al. 2002). The prevalence of subclinical thyroid dysfunction in various populations is 1.3-17.5% for subclinical hypothyroidism and 0.6-16% for subclinical hyperthyroidism; the reported rates depend on age, sex, iodine intake, sensitivity of measurements, and definition used (Biondi et al. 2002). Normal thyroid function requires sufficient intake of iodine (at least 100 micrograms/day [μg/d]), and areas of endemic iodine deficiency are associated with disorders such as endemic goiter and cretinism (Larsen et al. 2002; Larsen and Davies 2002; Goodman 2003). Iodine intake in the United States (where iodine is added to table salt) is decreasing (CDC 2002d; Larsen et al. 2002), and an estimated 12% of the population has low concentrations of urinary iodine (Larsen et al. 2002).

The principal regulator of thyroid function is the pituitary hormone thyroid-stimulating hormone (TSH), which in turn is controlled by positive input from the hypothalamic hormone thyrotropin-releasing hormone (TRH) and by negative input from T4 and T3. TSH binds to G-protein-coupled receptors in the surface membranes of thyroid follicular cells (Goodman 2003), which leads to increases in both the cyclic adenosine monophosphate (cAMP) and diacylglycerol/inositol trisphosphate second messenger pathways (Goodman 2003). T3, rather than T4, probably is responsible for the feedback response for TSH production (Schneider et al. 2001). Some T3, the active form of thyroid hormone, is secreted directly by the thyroid along with T4, but most T3 is produced from T4 by one of two deiodinases (Types I and II\(^1\)) in the peripheral tissue (Schneider et al. 2001; Larsen et al. 2002; Goodman 2003). T3 enters the nucleus of the target cells and binds to specific receptors, which activate specific genes.

**Background**

An effect of fluoride exposure on the thyroid was first reported approximately 150 years ago (Maumené 1854, 1866; as cited in various reports). In 1923, the director of the Idaho Public Health Service, in a letter to the Surgeon General, reported enlarged thyroids in many children between the ages of 12 and 15 using city water in the village of Oakley, Idaho (Almond 1923); in addition, the children using city water had severe enamel deficiencies in their permanent teeth. The dental problems were eventually attributed to the presence in the city water of 6 mg/L fluoride, and children born after a change in water supply (to water with <0.5 mg/L fluoride) were not

\(^1\)Type I deiodinase, along with Type III, is also responsible for deactivating T4 and T3 by removing the iodine atoms (Schneider et al. 2001; Larsen et al. 2002; Goodman 2003).
so affected (McKay 1933); however, there seems to have been no further report on thyroid conditions in the village.

More recently, Demole (1970) argued that a specific toxicity of fluoride for the thyroid gland does not exist, because (1) fluoride does not accumulate in the thyroid; (2) fluoride does not affect the uptake of iodine by thyroid tissue; (3) pathologic changes in the thyroid show no increased frequency in regions where water is fluoridated (naturally or artificially); (4) administration of fluoride does not interfere with the prophylactic action of iodine on endemic goiter; and (5) the beneficial effect of iodine in threshold dosage to experimental animals is not inhibited by administration of fluoride, even in excessive amounts. Bürgi et al. (1984) also stated that fluoride does not potentiate the consequences of iodine deficiency in populations with a borderline or low iodine intake and that published data fail to support the hypothesis that fluoride has adverse effects on the thyroid (at doses recommended for caries prevention). McLaren (1976), however, pointed out the complexity of the system, the difficulties in making adequate comparisons of the various studies of fluoride and the thyroid, and evidence for fluoride accumulation in the thyroid and morphological and functional changes (e.g., changes in activity of adenylyl cyclase), suggesting that analytical methods could have limited the definitiveness of the data to date. His review suggested that physiological or functional changes might occur at fluoride intakes of 5 mg/day.

Although fluoride does not accumulate significantly in most soft tissue (as compared to bones and teeth), several older studies found that fluoride concentrations in thyroid tissue generally exceed those in most other tissue except kidney (e.g., Chang et al. 1934; Hein et al. 1954, 1956); more recent information with improved analytic methods for fluoride was not located. Several studies have reported no effect of fluoride treatment on thyroid weight or morphology (Gedalia et al. 1960; Stolc and Podoba 1960; Saka et al. 1965; Bobek et al. 1976; Hara 1980), while others have reported such morphological changes as mild atrophy of the follicular epithelium (Ogilvie 1953), distended endoplasmic reticulum in follicular cells (Sundström 1971), and “morphological changes suggesting hormonal hypofunction” (Jonderko et al. 1983).

Fluoride was once thought to compete with iodide for transport into the thyroid, but several studies have demonstrated that this does not occur (Harris and Hayes 1955; Levi and Silberstein 1955; Anbar et al. 1959; Saka et al. 1965). The iodide transporter accepts other negatively charged ions besides iodide (e.g., perchlorate), but they are about the same size as iodide (Anbar et al. 1959); fluoride ion is considerably smaller and does not appear to displace iodide in the transporter.
Animal Studies

A number of studies have examined the effects of fluoride on thyroid function in experimental animals or livestock (for details, see Appendix E, Tables E-1, E-2, and E-3). Of these, the most informative are those that have considered both the fluoride and iodine intakes.

Guan et al. (1988) found that a fluoride intake of 10 mg/L in drinking water had little apparent effect on Wistar rats with sufficient iodine intake, but a fluoride intake of 30 mg/L in drinking water resulted in significant decreases in thyroid function (decreases in T4, T3, thyroid peroxidase, and 3H-leucine), as well as a decrease in thyroid weight and effects on thyroid morphology (Table E-2). In iodine-deficient rats, fluoride intake of 10 mg/L in drinking water produced abnormalities in thyroid function beyond that attributable to low iodine, including decreased thyroid peroxidase, and low T4 without compensatory transformation of T4 to T3.

Zhao et al. (1998), using male Kunmin mice, found that both iodine-deficient and iodine-excess conditions produced goiters, but, under iodine-deficient conditions, the goiter incidence at 100 days increased with increased intake of fluoride. At 100 days, the high-fluoride groups had elevated serum T4 at all concentrations of iodine intake and elevated T3 in iodine-deficient animals. High fluoride intake significantly inhibited the radioiodine uptake in the low- and normal-iodine groups.

Stolc and Podoba (1960) found a decrease in protein-bound iodine in blood in fluoride-treated female rats (3-4 mg/kg/day) fed a low-iodine diet but not in corresponding rats fed a larger amount of iodine. Both groups (low- and high-iodine) of fluoride-treated rats showed a reduced rate of biogenesis of T3 and T4 after administration of 131I compared with controls (Stolc and Podoba 1960).

Bobek et al. (1976) found decreases in plasma T4 and T3 as well as a decrease in free T4 index and an increase in T3-resin uptake in male rats given 0.1 or 1 mg of fluoride per day (0.4-0.6 or 4-6 mg/kg/day) in drinking water for 60 days. The authors suggested the possibility of decreased binding capabilities and altered thyroid hormone transport in blood.

Decreases in T4 and T3 concentrations have been reported in dairy cows at estimated fluoride doses up to 0.7 mg/kg/day with possible iodine deficiency (Hillman et al. 1979; Table E-3). Reduced T3 (Swarup et al. 1998) and reduced T3, T4, and protein-bound iodine (Cinar and Selcuk 2005) have also been reported in cows diagnosed with chronic fluorosis in India and Turkey, respectively.

2The decrease in T3 in the group receiving 0.1 mg/day was not statistically significant (Table E-1). Note that ATSDR (2003) stated that an intermediate-duration minimal risk level (MRL) derived from this study of thyroid effects in rats would have been lower (more protective) than the chronic-duration MRL derived from a human study of bone effects (0.05 mg/kg/day).
Hara (1980) found elevated T3 and T4 at the lowest dose (approximately 0.1 mg/kg/day), decreased T3 and normal T4 at intermediate doses (3-4 mg/kg/day), and decreased TSH and growth hormone (indicating possible effects on pituitary function) at the highest doses (10-20 mg/kg/day). This was the only animal study of fluoride effects on thyroid function to measure TSH concentrations; however, full details (e.g., iodine intake) are not available in English.

Other studies have shown no effect of fluoride on the end points examined (Gedalia et al. 1960; Siebenhüner et al. 1984; Clay and Suttie 1987; Choubisa 1999; Table E-1). Choubisa (1999) looked only for clinical evidence of goiter in domestic animals (cattle and buffaloes) showing signs of enamel or skeletal fluorosis; no hormone parameters (e.g., T4, T3, TSH) were measured. Gedalia et al. (1960) also did not measure T4, T3, or TSH; radioiodine uptake, protein-bound iodine, and total blood iodine were all normal in rats receiving fluoride doses up to approximately 1 milligram per kilogram of body weight per day (mg/kg/day). Clay and Suttie (1987) reported no significant differences from control values for T4 concentration and T3 uptake in heifers fed up to 1.4 mg/kg/day; iodine intake is not stated but probably was adequate, and TSH was not measured.

Siebenhüner et al. (1984) carried out a special experiment involving iodine depletion of the thyroid before 6 days of fluoride treatment. No effects were seen on the parameters measured, including T3 and T4 concentrations; however, TSH was not measured. In addition, propylthiouracil (PTU), the agent used to deplete the thyroid of iodine, also has an inhibitory effect on deiodinases (Larsen et al. 2002; Larsen and Davies 2002); Siebenhüner et al. (1984) did not mention this second action of PTU and its relevance to the interpretation of the experimental results, and there was no control group without the PTU treatment.

Human Studies

Several authors have reported an association between endemic goiter and fluoride exposure or enamel fluorosis in human populations in India (Wilson 1941; Siddiqui 1960; Desai et al. 1993), Nepal (Day and Powell-Jackson 1972), England (Wilson 1941; Murray et al. 1948), South Africa (Steyn 1948; Steyn et al. 1955; Jooste et al. 1999), and Kenya (Obel 1982). Although endemic goiter is now generally attributed to iodine deficiency (Murray et al. 1948; Obel 1982; Larsen et al. 2002; Belchetz and Hammond 2003), some of the goitrogenic areas associated with fluoride exposure were not considered to be iodine deficient (Steyn 1948; Steyn et al. 1955; Obel 1982; Jooste et al. 1999). Obel (1982) indicated that many cases of fluorosis in Kenya occur concurrently with goiter. Several authors raise the possibility that the goitrous effect, if not due to fluoride, is due to some other substance.
in the water (e.g., calcium or water hardness) that was associated with the fluoride concentration (Murray et al. 1948; Day and Powell-Jackson 1972) or that enhanced the effect of fluoride (Steyn 1948; Steyn et al. 1955). Dietary selenium deficiencies (e.g., endemic in parts of China and Africa or due to protein-restricted diets) can also affect normal thyroid function\(^3\) (Larsen et al. 2002); no information on dietary selenium is available in any of the fluoride studies. Appendix E summarizes a number of studies of the effects of fluoride on thyroid function in humans (see Table E-4).

Three studies illustrated the range of results that have been reported: (1) Gedalia and Brand (1963) found an association between endemic goiter in Israeli girls and iodine concentrations in water but found no association with fluoride concentrations (<0.1-0.9 mg/L). (2) Siddiqui (1960) found goiters only in persons aged 14-17 years; the goiters, which became less visible or invisible after puberty, were associated with mean fluorine content of the water (5.4-10.7 mg/L) and were inversely associated with mean iodine content of the water. (3) Desai et al. (1993) found a positive correlation \(P < 0.001\) between prevalence of goiter (9.5-37.5\%) and enamel fluorosis (6.0-59.0\%), but no correlation between prevalence of goiter and water iodine concentration \(P > 0.05\).

Day and Powell Jackson (1972) surveyed 13 villages in Nepal where the water supply was uniformly low in iodine (≤1 µg/L; see Figure 8-1). Here the goiter prevalence (5-69\%, all age groups) was directly associated with the fluoride concentration (<0.1 to 0.36 mg/L; \(P < 0.01\)) or with hardness, calcium concentration, or magnesium concentration of the water (all \(P < 0.01\)). Goiter prevalence of at least 20\% was associated with all fluoride concentrations ≥ 0.19 mg/L, suggesting that fluoride might influence the prevalence of goiter in an area where goiter is endemic because of low iodine intake. The possibility of a nutritional component (undernutrition or protein deficiency) to the development of goiter was also suggested.

Jooste et al. (1999) examined children (ages 6, 12, and 15) who had spent their entire lives in one of six towns in South Africa where iodine concentrations in drinking water were considered adequate (median urinary iodine concentration exceeding 201 µg/L \[1.58 \mu mol/L\]; see Appendix E, Tables E-4 and E-5; Figure 8-2). For towns with low (0.3-0.5 mg/L) or near “optimal” (0.9-1.1 mg/L) fluoride concentrations in water, no relationship between fluoride and prevalence of mild goiter was found (5-18\%); for the other two towns (1.7 and 2.6 mg/L fluoride), however, goiter prevalences were 28\% and 29\%, respectively, and most children had severe enamel mottling. These two towns (and one low-fluoride town) had very low proportions (0-2.2\%) of children with iodine deficiency, defined as urinary

\(^3\)All three deiodinases contain selenocysteine at the active sites and therefore have a minimum requirement for selenium for normal function (Larsen et al. 2002).
FIGURE 8-1  Goiter prevalence versus fluoride (left) and calcium (right) concentration in drinking water for 13 villages in Nepal with very low iodine concentrations. SOURCE: Day and Powell-Jackson 1972.

iodine concentrations <100 µg/L (<0.79 µmol/L). The town with the lowest prevalence of goiter also had the lowest prevalence of undernutrition; the two towns with the highest prevalence of goiter (and highest fluoride concentrations) did not differ greatly from the remaining three towns with

FIGURE 8-2  Goiter prevalence versus drinking water fluoride concentrations in six South African towns with adequate iodine concentrations. One town had a significantly lower prevalence of undernutrition than the other five towns and is not included in the line fitting. SOURCE: Jooste et al. 1999.
respect to prevalence of undernutrition. The authors suggested that fluoride or an associated goitrogen might be responsible for the goiters seen in the two towns with the highest fluoride concentrations but that some other factor(s) was involved in development of goiter in the other towns.

Several studies have compared various aspects of thyroid status in populations with different fluoride intakes (for details, see Appendix E, Table E-4). Leone et al. (1964) and Baum et al. (1981) reported no significant differences in thyroid status between populations with low (0.09-0.2 mg/L) and high (3-3.5 mg/L) fluoride concentrations in the drinking water. Leone et al. (1964) looked only at protein-bound iodine and physical examination of the thyroid in adults; Baum et al. (1981) measured a number of parameters in teenagers, including T4, T3, and TSH. Neither study reported iodine status of the groups. Baum et al. (1981) showed but did not explain a decrease in thyroglobulin in girls in the high-fluoride group.

Bachinskii et al. (1985) examined 47 healthy persons, 43 persons with hyperthyroidism, and 33 persons with hypothyroidism. Prolonged consumption of “high-fluoride” drinking water (2.3 mg/L, as opposed to “normal” concentrations of 1 mg/L) by healthy persons was associated with statistically significant changes in TSH concentrations (increased), T3 concentrations (decreased), and uptake of radioiodine (increased), although the mean values for TSH and T3 were still within normal ranges (see Appendix E, Table E-6). The mean value of TSH for the healthy group (4.3 ± 0.6 milliunits/L; Table E-6) is high enough that one expects a few individuals to have been above the normal range (typically 0.5-5 milliunits/L; Larsen et al. 2002). These results were interpreted as indicating disruption of iodine metabolism, stress in the pituitary-thyroid system, and increased risk of developing thyroidopathy (Bachinskii et al. 1985).

Lin et al. (1991) examined 769 children (7-14 years old) for mental retardation in three areas of China, including an area with “high” fluoride (0.88 mg/L) and low iodine, an area with “normal” fluoride (0.34 mg/L) and low iodine, and an area where iodine supplementation was routine (fluoride concentration not stated). Ten to twelve children in each area received detailed examinations, including measuring thyroid 131I uptake and thyroid hormone concentrations. Children in the first area had higher TSH, slightly higher 131I uptake, and lower mean IQ than children in the second area. Children in the first area also had reduced T3 and elevated reverse T3, compared with children in the second area. The authors suggested that high fluoride might exacerbate the effects of iodine deficiency. In addition, the authors reported a difference in T3/rT3 (T3/reverse-T3) ratios between high- and low-fluoride areas and suggested that excess fluoride ion affects normal deiodination.

A recent study by Susheela et al. (2005) compared thyroid hormone status (free T4, free T3, and TSH) of 90 children with enamel fluorosis
(drinking water fluoride ranging from 1.1 to 14.3 mg/L) and 21 children without enamel fluorosis (0.14-0.81 mg/L fluoride in drinking water) in areas where iodine supplementation was considered adequate.\textsuperscript{4} Forty-nine children (54.4\%) in the sample group had "well-defined hormonal derangements"; findings were borderline in the remaining 41 children. The types of hormonal derangements included elevated TSH and normal T4 and T3 (subclinical hypothyroidism); low T3 and normal T4 and TSH ("low T3 syndrome"); elevated T3 and TSH and normal T4 (possible T3 toxicosis); elevated TSH, low T4, and normal T3 (usually indicative of primary hypothyroidism and iodine deficiency); and low T3, high TSH, and normal T4. All but the first category are considered to be associated with or potentially caused by abnormal activity of deiodinases. The authors concluded that fluoride in excess may be inducing diseases that have usually been attributed to iodine deficiency and that iodine supplementation may not be adequate when excess fluoride is being consumed.

Thyroid hormone disturbances were also noted in the control children, and urine and fluoride concentrations in the control children reflect higher fluoride intake than can be accounted for by the drinking water alone (Susheela et al. 2005). Thus, the authors recommend that end points such as hormone concentrations should be examined with respect to serum or urinary fluoride concentrations, not just drinking water fluoride concentrations. In addition, they note that all hormone endpoints (T3, T4, and TSH) should be examined, lest some of the abnormalities be missed.

Mikhailet\textsuperscript{s} et al. (1996) detected thyroid abnormalities (moderate reduction of iodine uptake, low T3, normal T4, and increased TSH) in 165 aluminum workers with signs of chronic fluorosis and an estimated average fluoride intake of 10 mg/working day. A tendency toward increased TSH was observed with increased exposure time and with more severe fluorosis. Workers with more than 10 years of service had a significant decrease in T3 concentration in comparison to controls. The frequency of individuals with low concentrations of T3 (corresponding to hypothyroidism) was 65\% among workers with more than 10 years of service and 54\% among workers with Stage 2 fluorosis. The highest frequency of occurrence of low T3 (76\%) was observed in people with chronic fluoride intoxication including liver damage (moderate cytolysis), suggesting a disorder in peripheral conversion of T4 to T3 (deiodination). The possibility of indirect effects of fluorine on enzymatic deiodination was also suggested.

Tokar\textsuperscript{\prime} et al. (1989) and Balabolkin et al. (1995) have also reported

\textsuperscript{4}The lower range of fluoride in drinking water in the fluorosis group is not much different from the higher range for the controls; however, in India, fluoride concentrations below 1 mg/L in drinking water are considered "safe" (Trivedi et al. 1993; Susheela et al. 2005) so the demarcation is at least a logical one.
thyroid effects in fluoride- or fluorine-exposed workers; full details of these studies are not available in English. Balabolkin et al. (1995) found that 51% of the workers examined had subclinical hypothyroidism with reduced T3.

No changes in thyroid function were detected in two studies of osteoporosis patients treated with NaF for 6 months or several years (Eichner et al. 1981; Hasling et al. 1987; for details, see Appendix E, Table E-7). These study populations are not necessarily representative of the general population, especially with respect to age and the fact that they usually receive calcium supplements. In an earlier clinical study to examine the reported effects of fluoride on individuals with hyperthyroidism, Galletti and Joyet (1958) found that, in 6 of 15 patients, both basal metabolic rate and protein-bound iodine fell to normal concentrations, and the symptoms of hyperthyroidism were relieved after fluoride treatment. Fluoride was considered clinically ineffective in the other 9 patients, although improvement in basal metabolic rate or protein-bound iodine was observed in some of them. In the 6 patients for whom fluoride was effective, tachycardia and tremor disappeared within 4-8 weeks, and weight loss was stopped. The greatest clinical improvement was observed in women between 40 and 60 years old with a moderate degree of thyrotoxicosis; young patients with the classic symptoms of Graves’ disease did not respond to fluoride therapy. Radioiodine uptake tests were performed on 10 of the patients, 7 of whom showed an inhibitory effect on initial $^{131}$I uptake by the thyroid.

Discussion (Effects on Thyroid Function)

In studies of animals with dietary iodine sufficiency, effects on thyroid function were seen at fluoride doses of 3-6 mg/kg/day (Stolc and Podoba 1960; Bobek et al. 1976; Guan et al. 1988; Zhao et al. 1998); in one study, effects were seen at doses as low as 0.4-0.6 mg/kg/day (Bobek et al. 1976). In low-iodine situations, more severe effects on thyroid function were seen at these doses (Stolc and Podoba 1960; Guan et al. 1988; Zhao et al. 1998). Effects on thyroid function in low-iodine situations have also been noted at fluoride doses as low as 0.06 mg/kg/day (Zhao et al. 1998), $\leq$0.7 mg/kg/day (Hillman et al. 1979), and 1 mg/kg/day (Guan et al. 1988). Studies showing no effect of fluoride on thyroid function did not measure actual hormone concentrations (Gedalia et al. 1960; Choubisa 1999), did not report iodine intakes (Gedalia et al. 1960; Clay and Suttie 1987; Choubisa 1999), used fluoride doses (<1.5 mg/kg/day) below those (3-6 mg/kg/day) associated with effects in other studies (Gedalia et al. 1960; Clay and Suttie 1987), or did not discuss a possibly complicating factor of the experimental procedure used (Siebenhüner et al. 1984). Only one animal study (Hara 1980) measured TSH concentrations, although that is considered a “precise and
specific barometer” of thyroid status in most situations (Larsen et al. 2002). Full details of Hara’s report are not available in English.

Goiter prevalence of at least 20% has been reported in humans exposed to water fluoride concentrations ≥ 0.2 mg/L (low-iodine situation; Day and Powell-Jackson 1972) or 1.5-3 mg/L (undernutrition, but adequate iodine; Jooste et al. 1999); however, other causes of goiter have not been ruled out. Bachinskii et al. (1985) showed increased TSH concentrations and reduced T3 concentrations in a population with a fluoride concentration of 2.3 mg/L in their drinking water (in comparison to a group with 1.0 mg/L), and Lin et al. (1991) showed similar results for a population with 0.88 mg/L fluoride in the drinking water (in comparison to a group with 0.34 mg/L); another study showed no effect at 3 mg/L (Baum et al. 1981). Among children considered to have adequate iodine supplementation, Susheela et al. (2005) found derangements of thyroid hormones in 54% of children with enamel fluorosis (1.1-14.3 mg/L fluoride in drinking water), and in 45-50% of “control” children without enamel fluorosis but with elevated serum fluoride concentrations. Mikhailets et al. (1996) observed an increase in TSH in workers with increased exposure time and with more severe fluorosis; low T3 was found in 65% of workers with more than 10 years of service and in 54% of workers with Stage 2 fluorosis. Several studies do not include measurements of T4, T3, or TSH (Siddiqui 1960; Gedalia and Brand 1963; Leone et al. 1964; Day and Powell-Jackson 1972; Teotia et al. 1978; Desai et al. 1993; Jooste et al. 1999).

Nutritional information (especially the adequacy of iodine and selenium intake) is lacking for many (iodine) or all (selenium) of the available studies on humans. As with the animal studies, high fluoride intake appears to exacerbate the effects of low iodine concentrations (Day and Powell-Jackson 1972; Lin et al. 1991). Uncertainty about total fluoride exposures based on water fluoride concentrations, variability in exposures within population groups, and variability in response among individuals generally have not been addressed. Although no thyroid effects were reported in studies using controlled doses of fluoride for osteoporosis therapy, the study populations are not necessarily representative of the general population with respect to age, calcium intake, and the presence of metabolic bone disease.

Thus, several lines of information indicate an effect of fluoride exposure on thyroid function. However, because of the complexity of interpretation of various parameters of thyroid function (Larsen et al. 2002), the possibility of peripheral effects on thyroid function instead of or in addition to direct effects on the thyroid, the absence of TSH measurements in most of the animal studies, the difficulties of exposure estimation in human studies, and the lack of information in most studies on nutritional factors (iodine, selenium) that are known to affect thyroid function, it is difficult to predict...
exactly what effects on thyroid function are likely at what concentration of fluoride exposure and under what circumstances.

Suggested mechanisms of action for the results reported to date include decreased production of thyroid hormone, effects on thyroid hormone transport in blood, and effects on peripheral conversion of T4 to T3 or on normal deiodination processes, but details remain uncertain. Both peripheral conversion of T4 to T3 and normal deiodination (deactivation) processes require the deiodinases (Types I and II for converting T4 to T3 and Types I and III for deactivation; Schneider et al. 2001; Larsen et al. 2002; Goodman 2003). Several sets of reported results are consistent with an inhibiting effect of fluoride on deiodinase activity; these effects include decreased plasma T3 with normal or elevated T4 and TSH and normal T3 with elevated T4 (Bachinskii et al. 1985; Guan et al. 1988; Lin et al. 1991; Balabolkin et al. 1995; Michael et al. 1996; Mikhailets et al. 1996; Susheela et al. 2005). The antihyperthyroid effect that Galletti and Joyet (1958) observed in some patients is also consistent with an inhibition of deiodinase activity in those individuals.

The available studies have generally dealt with mean values of various parameters for the study groups, rather than with indications of the clinical significance, such as the fraction of individuals with a value (e.g., TSH concentration) outside the normal range or with clinical thyroid disease. For example, in the two populations of asymptomatic individuals compared by Bachinskii et al. (1985), the elevated mean TSH value in the higher-fluoride group is still within the normal range, but the number of individuals in that group with TSH values above the normal range is not given.

In the absence of specific information in the reports, it cannot be assumed that all individuals with elevated TSH or altered thyroid hormone concentrations were asymptomatic, although many might have been. For asymptomatic individuals, the significance of elevated TSH or altered thyroid hormone concentrations is not clear. Belchetz and Hammond (2003) point out that the population-derived reference standards (e.g., for T4 and TSH) reflect the mean plus or minus two standard deviations, meaning that 5% of normal people have results outside a given range. At the same time, healthy individuals might regulate plasma T4 within a “personal band” that could be much more narrow than the reference range; this brings up the question of whether a disorder shifting hormone values outside the personal band but within the population reference range requires treatment (Davies and Larsen 2002; Belchetz and Hammond 2003). For example, early hypothyroidism can present with symptoms and raised TSH but with T4 concentrations still within the reference range (Larsen et al. 2002; Belchetz and Hammond 2003).

Subclinical hypothyroidism is considered a strong risk factor for later
development of overt hypothyroidism (Weetman 1997; Helfand 2004). Biondi et al. (2002) associate subclinical thyroid dysfunction (either hypo-
or hyperthyroidism) with changes in cardiac function and corresponding increased risks of heart disease. Subclinical hyperthyroidism can cause bone demineralization, especially in postmenopausal women, while subclinical hypothyroidism is associated with increased cholesterol concentrations, increased incidence of depression, diminished response to standard psychiatric treatment, cognitive dysfunction, and, in pregnant women, decreased IQ of their offspring (Gold et al. 1981; Brucker-Davis et al. 2001). Klein et al. (2001) report an inverse correlation between severity of maternal hypothyroidism (subclinical or asymptomatic) and the IQ of the offspring (see also Chapter 7).

A number of authors have reported delayed eruption of teeth, enamel defects, or both, in cases of congenital or juvenile hypothyroidism (Hinrichs 1966; Silverman 1971; Biggerstaff and Rose 1979; Noren and Alm 1983; Loevy et al. 1987; Bhat and Nelson 1989; Mg’ang’a and Chindia 1990; Pirinen 1995; Larsen and Davies 2002; Hirayama et al. 2003; Ionescu et al. 2004). No information was located on enamel defects or effects on eruption of teeth in children with either mild or subclinical hypothyroidism. The possibility that either dental fluorosis (Chapter 4) or the delayed tooth eruption noted with high fluoride intake (Chapter 4; see also Short 1944) may be attributable at least in part to an effect of fluoride on thyroid function has not been studied.

THYROID PARAFOLLICULAR CELLS

The parafollicular cells (C cells) of the thyroid produce a 32-amino acid peptide hormone called calcitonin (Bringhurst et al. 2002; Goodman 2003). Calcitonin acts to lower blood calcium and phosphate concentrations, primarily or exclusively by inhibiting osteoclastic (bone resorption) activity. Calcitonin does not play a major role in calcium homeostasis in humans, and its primary importance seems to be to protect against excessive bone resorption (Bringhurst et al. 2002; Goodman 2003). At high concentrations, calcitonin can also increase urinary excretion of calcium and phosphate, but these effects in humans are small and not physiologically important for lowering blood calcium (Goodman 2003). Parafollicular cells express the same G-protein-coupled, calcium-sensing receptors in their surface membranes as do the chief cells of the parathyroid glands, receptors that respond directly to ionized calcium in blood; however, the secretory response of the parafollicular cells is opposite that of the parathyroid chief cells (Bringhurst et al. 2002; Goodman 2003).
Animal Studies

Very few animal studies have examined the effects of fluoride exposure on parafollicular cells or calcitonin secretion (see Appendix E, Table E-8). Sundström (1971) found no evidence for short-term release of calcitonin in response to fluoride treatment in rats, in line with the view that NaF administration to rats by lavage resulted in hyperparathyroidism, secondary to the calcitonin-like (blood calcium-lowering) action of fluoride on bone tissue. Rantanen et al. (1972) reported that fluoride exposure had a retarding effect on cortical bone remodeling in female pigs and that an intact thyroid gland was necessary for this effect. Replacing thyroid hormone (but not calcitonin) in thyroidectomized pigs eliminated the retarding effect of fluoride, suggesting that the effect involved the formation, release, or enhanced action of calcitonin.

Human Studies

Teotia et al. (1978) found elevated calcitonin concentrations in seven patients with skeletal fluorosis in a high-fluoride area and in one of two patients who had moved to low-fluoride areas and showed improvement in various parameters (see Appendix E, Tables E-9 and E-10). Elevated calcitonin was found in all patients with an estimated fluoride intake of at least 9 mg/day and in one patient with an estimated current fluoride intake of 3.8 mg/day and a previous (until 2 years before) intake of 30 mg/day. Four of the individuals also had elevated parathyroid hormone (PTH), and radiographs of two suggested secondary hyperparathyroidism. Plasma calcium in the fluorosis patients was generally in the normal range, but urinary calcium concentrations were lower than those of controls; dietary calcium intakes were considered to be adequate. Vitamin D deficiency was not found.

In a review of skeletal fluorosis, Krishnamachari (1986) mentioned, but did not elaborate on, “significant alterations” in the “parathyroid-thyrocalcitonin axis,” also stating that the sequence of the hormonal changes was not clear and that the changes did not occur to the same degree in all patients, possibly reflecting the adequacy of calcium intake. Elevated calcitonin was found in some but not all cases of skeletal fluorosis in a series of epidemiologic studies reviewed by Teotia et al. (1998).

Tokar’ et al. (1989) reported elevated concentrations of calcitonin in the blood of workers employed in fluorine production, indicating stimulation of thyroid gland parafollicular cells. Huang et al. (2002) reported significantly elevated concentrations of serum PTH and calcitonin in 50 male fluoride workers and concluded that an excess of fluoride might affect secretion of both calcium-adjusting hormones.
Discussion (Effects on Parafollicular Cell Function)

Calcitonin concentrations do not seem to have been routinely measured in cases of skeletal fluorosis, but elevated calcitonin does seem to be present when looked for. The effect has been noted at fluoride intakes as low as 3.8 mg/day in humans (approximately 0.06 mg/kg/day) and was found routinely at intakes of at least 9 mg/day (approximately 0.15 mg/kg/day). No animal studies have reported calcitonin concentrations after fluoride exposure. Teotia et al. (1978) proposed several possible mechanisms (direct and indirect) of fluoride action with respect to effects on calcitonin and PTH secretion, but currently the significance of the elevated calcitonin concentrations associated with skeletal fluorosis is not clear.  

PARATHYROID GLANDS

In humans, four small parathyroid glands are normally situated on the posterior surface of the thyroid. These glands produce PTH, a simple 84-peptide hormone, which is the principal regulator of extracellular calcium (Brinaghurst et al. 2002; Goodman 2003). The primary effect of PTH is to increase the calcium concentration and decrease the phosphate concentration in blood (Brinaghurst et al. 2002; Goodman 2003). The major mechanisms by which this effect occurs include the mobilization of calcium phosphate from the bone matrix, primarily from increased osteoclastic activity; in the kidney, increased reabsorption of calcium, decreased reabsorption of phosphate, and increased activation of vitamin D; and increased intestinal absorption of calcium (Brinaghurst et al. 2002; Goodman 2003). PTH is also important for skeletal homeostasis (bone remodeling). Regulation of PTH secretion is inversely related to the concentration of ionized calcium (Brinaghurst et al. 2002; Goodman 2003).

Healthy individuals secrete PTH throughout the day (1-3 pulses per hour); blood concentrations of PTH also exhibit a diurnal pattern, with peak values after midnight and minimum values in late morning (el-Hajj

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5Calcitonin inhibits bone resorption by acting directly on the osteoclast, but it appears to play only a small role in regulating bone turnover in adults (Raisz et al. 2002). Elevated calcitonin concentrations are often present in certain types of malignancy, especially medullary thyroid carcinoma (carcinoma arising from the thyroid parafollicular cells; Brinaghurst et al. 2002; Schlumberger et al. 2002), but are considered a marker for the malignancy or for certain other severe illnesses, rather than an adverse consequence. One source suggests that subtle alterations in calcitonin production or response may play a role in metabolic bone disease (Raisz et al. 2002).

6It is important to note that assays of PTH have varied over the years (Brinaghurst et al. 2002; Goodman 2003), making it difficult to compare reported PTH concentrations among different studies; in this report, PTH concentrations (when given) are compared with the controls or healthy individuals reported for the specific studies.
Fuleihan et al. 1997; Goodman 2003). Circadian patterns of PTH concentrations differ in men and women (Calvo et al. 1991) and between healthy and osteoporotic postmenopausal women (Eastell et al. 1992; Fraser et al. 1998). The diurnal fluctuations might be important for urinary calcium conservation (el-Hajj Fuleihan et al. 1997) and might be involved in anabolic responses of bone to PTH (Goodman 2003). Alterations in PTH rhythms might contribute to or be associated with osteoporosis (el-Hajj Fuleihan et al. 1997; Fraser et al. 1998).

**In Vitro Studies**

Fluoride ion has been shown to be a potent inhibitor of PTH secretion in bovine and human parathyroid cells in vitro (Chen et al. 1988; Shoback and McGhee 1988; Sugimoto et al. 1990; Ridefelt et al. 1992); PTH inhibition was observed at concentrations ranging from 0.5 to 20 mM (9.5-380 mg/L) with maximum effect at or above 5 mM (95 mg/L). This action by fluoride either requires or is potentiated by Al$^3+$, consistent with a mechanism of G-protein stimulation. Fluoride (or aluminum fluoride), via the G proteins, suppresses cAMP accumulation, increases cytosolic Ca$^{2+}$ (probably by stimulating a calcium channel), increases inositol phosphate accumulation, and also might directly inhibit the PTH secretory process (Chen et al. 1988; Shoback and McGhee 1988; Sugimoto et al. 1990; Ridefelt et al. 1992). No single mechanism is clearly responsible for inhibiting PTH secretion, suggesting that several mechanisms might be involved in its regulation.

**Animal Studies**

A number of animal studies of the effects of fluoride on parathyroid function are summarized below (for more details, see Appendix E, Table E-11). Administration of NaF as a lavage was found to elicit hyperparathyroidism in rats (Yates et al. 1964, as cited by Sundström 1971); the hyperparathyroidism was thought to be secondary to a direct, calcitonin-like, action of fluoride on bone tissue (Rich and Feist 1970, as cited by Sundström 1971). Levy et al. (1970) demonstrated increased resistance (suppressed sensitivity) of alveolar bone to PTH (in pharmacologic doses) in marmosets fed fluoride in drinking water (50 mg/L) for 5 months. More recently, increased serum inorganic fluoride due to use of the anesthetic isoflurane was associated with decreased ionized calcium and increased PTH and osteocalcin in cynomolgus monkeys (Hotchkiss et al. 1998).

A fivefold increase in blood PTH was seen as early as 1 week in lambs given drinking water with fluoride at 90 mg/L (Faccini and Care 1965); by 1 month, ultrastructural changes considered to be indicative of increased activity were observed in the parathyroid glands. The overactivity of the
parathyroid might be a response to a “more stable mineral system, i.e. fluoroapatite” that is “resistant to the normal processes of resorption,” thus requiring an increase in PTH activity to maintain normal serum calcium concentrations (Faccini 1969).

Chavassieux et al. (1991) reported a significant decrease in serum calcium and phosphorus and increases in serum PTH in sheep fed 1 or 5 mg of NaF per kg per day for 45 days, without calcium supplementation. Because of wide variation, the increased serum PTH is not considered statistically significant, but mean serum PTH in both groups at 45 days was at least twice as high as at the beginning of the experiment. This study and those of Faccini and Care (1965) and Hotchkiss et al. (1998) suggest a hypocalcemic response to the fluoride, followed by increased PTH secretion in response to the hypocalcemia.

Two longer-term animal studies with “high” concentrations of calcium and vitamin D intake have reported no effect of fluoride exposure on calcium homeostasis or parathyroid function (Andersen et al. 1986; Turner et al. 1997). However, two other studies with low-calcium situations found an altered parathyroid response. In one of these studies, Li and Ren (1997) reported that rats fed fluoride (100 mg/L in drinking water) for 2 months along with a low-calcium diet exhibited osteomalacia, osteoporosis, accelerated bone turnover, increased serum alkaline phosphatase, increased osteocalcin, and increased PTH. Fluoride-treated animals with adequate dietary calcium showed only slightly increased osteoblastic activity after 2 months but elevated serum alkaline phosphatase activity and increased average width of trabecular bone after 1 year.

In an earlier study, Rosenquist et al. (1983) fed drinking water containing fluoride at 50 mg/L to male Wistar rats from the age of 5 weeks until age 51 weeks; half the animals were given a calcium-deficient diet for the last 16 weeks. Control animals were fed drinking water containing fluoride at <0.5 mg/L. At 35 weeks, average serum immunoreactive PTH was reduced, but not significantly, in the fluoride-treated rats. At 51 weeks, calcium-deficient rats without fluoride showed elevated PTH (the normal response), whereas calcium-deficient rats with fluoride showed very slightly less PTH than calcium-sufficient, fluoride-treated rats. All groups had normal serum calcium concentrations. The authors concluded that fluoride in the amount used does not increase parathyroid activity and that fluoride supplementation “seems to prevent the profound changes in parathyroid activity that result from calcium deficiency” (Rosenquist et al. 1983). However, a better interpretation of the data is that the normal increase in PTH in response to a dietary calcium deficiency did not occur in the fluoride-treated animals.

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7Elevated osteocalcin and alkaline phosphatase are considered markers for bone turnover (Raisz et al. 2002).
(although some morphological changes occurred), suggesting that normal parathyroid function was inhibited. These animals were adults when the calcium deficiency was imposed, and the effect of fluoride treatment on animals with a preexisting calcium deficiency was not examined. Substantially wider standard deviations were observed for all fluoride-treated and calcium-deficient groups than in the controls (no fluoride, calcium sufficiency), suggesting variable responses in the animals.

Dunipace et al. (1995, 1998) examined the effects of fluoride (up to 50 mg/L in drinking water) on male Sprague-Dawley rats with a normal diet (Dunipace et al. 1995) or with either a calcium-deficient diet or a diet deficient in protein, energy, or total nutrients (Dunipace et al. 1998). Fluoride reportedly had no effect on various clinical parameters monitored in normal, calcium-deficient, or malnourished animals; however, the papers showed results only for combinations of fluoride treatment groups, and calcium-related parameters such as PTH and calcitonin concentrations were not measured. The combination of general malnutrition and calcium deficiency was not examined.

Verma and Guna Sherlin (2002b) reported hypocalcemia in female rats and their offspring when the mothers were treated with NaF (40 mg/kg/day) during gestation and lactation. PTH was not measured.

Tiwari et al. (2004) reported decreased serum calcium, increased serum alkaline phosphatase, increased concentrations of vitamin D metabolites (both 25(OH)D3 and 1,25(OH)2D3), and lower whole body bone mineral density (suggestive of deficient mineralization) in rats born to mothers given a calcium-deficient diet and high fluoride (50 mg/L in drinking water) from day 11 of gestation; after weaning the pups were given the same low-calcium, high-fluoride regimen. Although the authors did not measure PTH or examine bone histomorphometry, they did demonstrate specific changes in gene transcription in the duodenal mucosa, including decreased transcription of the genes for the vitamin D receptor and calbindin D 9 k (a vitamin-D regulated protein that enhances calcium uptake) and altered (decreased at 9 weeks) transcription of the gene for the calcium-sensing receptor (which senses changes in extracellular calcium concentrations and regulates serum calcium concentrations by influencing PTH secretion). Excess fluoride continued to produce alterations in gene expression even when calcium was restored to the diet. The changes in gene expression are thought to result in decreased absorption of calcium from the gut.

Human Studies (Clinical, Occupational, or Population)

Clinical, occupational, and population studies of the effects of fluoride on human parathyroid function are summarized below (for more detail, see Appendix E, Table E-12). In one study with healthy subjects, a single oral
dose of 27 mg of fluoride was followed by decreases in serum calcium and phosphorus and an increase in serum immunoreactive PTH (Larsen et al. 1978), suggesting a rise in PTH in response to the decrease in serum calcium. The fall in serum calcium was attributed to increased mineralization of bone in response to the fluoride dose. Oral doses of fluoride at 27 mg/day for 3 weeks in healthy adults produced a significant increase in serum osteocalcin at the end of the 3-week period but not in total or ionized calcium, alkaline phosphatase, PTH, and several other parameters (Dandona et al. 1988). The mean PTH concentration at 3 weeks was elevated slightly over the initial (pretreatment) values, and the standard deviation was considerably larger, suggesting that a few individuals might have had significant increases. In a follow-up letter, Gill et al. (1989) suggested that the age of the subjects and the sensitivity of the PTH assay might influence the findings.

Stamp et al. (1988, 1990) reported increased concentrations of biologically active PTH in osteoporosis patients receiving both calcium and sodium fluoride during short- and long-term treatments. In the short-term (8-day) study, two groups of patients were identified with respect to stability of serum calcium and phosphorus concentrations (Stamp et al. 1988). In the group with more stable serum calcium, NaF inhibited intestinal calcium and phosphorus absorption and reduced calcium balance; this inhibition is not explainable by the formation of calcium-fluoride complexes and might be due to inhibition by fluoride of some step(s) in active transport (Stamp et al. 1988).

In patients treated for 15 ± 10 months, the treated group as a whole had statistically significant elevation of biologically active PTH and serum alkaline phosphatase (Stamp et al. 1990). In those patients (32% of the treated group) in whom biologically active PTH was above the upper limit of normal, serum alkaline phosphatase was not elevated above control concentrations; elevated PTH also was associated with relative hypophosphatemia and relative hypercalciuria. Thus, in some individuals, fluoride stimulated the synthesis or release of serum alkaline phosphatase, and PTH concentrations were in the normal range; in others, serum alkaline phosphatase was not increased, indicating failure of the osteoblastic response, and PTH concentrations were above the normal range.

Duursma et al. (1987) also found that individuals varied in their responses to fluoride treatment for osteoporosis. Those individuals who had a femoral neck fracture during the treatment period (6 of 91 patients) also appeared to have lower serum alkaline phosphatase concentrations and higher serum PTH concentrations than other patients.

In a comparison of 25 fluoride-treated osteoporosis patients with calcium supplementation and 38 controls with no fluoride treatment (but in most cases calcium supplementation), Jackson et al. (1994) reported no significant difference in mean calcium concentrations between groups,
although 2 of 25 individuals were outside the normal range (versus 0 of 38 controls). A significant elevation in mean alkaline phosphatase concentration was observed in the treated group, with 8 of 25 individuals outside the normal range (versus 0 of 38 controls); for those 8 individuals, the significant elevation was largely due to an increased concentration of bone isoenzymes. For the 24 patients for whom baseline (pretreatment) information was available, mean calcium concentrations were significantly lower and alkaline phosphatase was significantly higher. PTH was not measured in these patients, and individuals with a history of thyroid, parathyroid, or gastrointestinal problems were not included in the study. The authors stated that “none of the mean differences between groups were considered to be clinically significant,” but whether some individuals had clinically significant situations was not addressed.

Dure-Smith et al. (1996) reported that fluoride-treated osteoporosis patients who showed a rapid increase in spinal bone density also showed a general state of calcium deficiency and secondary hyperparathyroidism; similarly treated patients with a decrease or slow increase in spinal bone density were much less likely to be calcium deficient. The degree of calcium deficiency appeared to be related to the previous fluoride-dependent increase in spinal bone density, indicating that an osteogenic response to fluoride can increase the skeletal requirement for calcium, even in patients with a high calcium intake. Reasons for the differences in response to fluoride treatment (rapid increase versus decrease or slow increase in spinal bone density) were not identified.

Osteoporosis patients treated either with slow-release NaF or with a placebo (both with concurrent calcium supplementation) showed decreases in immunoreactive PTH from initial pretreatment values, presumably due to the calcium supplementation (Zerwekh et al. 1997b). PTH values in the fluoride-treated group stayed slightly (but not significantly) higher than those in the placebo group.

Li et al. (1995) described a population study in China that examined adults in regions with various fluoride concentrations in the drinking water and either “normal” or “inadequate” nutrition in terms of protein and calcium intake; people in the sample were “healthy” rather than randomly selected. A significant decrease in blood calcium concentration was associated with an increase in fluoride exposure in the populations with inadequate nutrition but was not detected in subjects with normal nutrition. Elevated alkaline phosphatase activity with increased fluoride exposure was observed in all populations, with higher values in subjects with inadequate nutrition. PTH concentrations were not measured. For calcium, alkaline phosphatase, and several other blood parameters, all values were stated to be within the normal range regardless of fluoride exposure and nutritional condition, but it is not clear whether “all values” refers to mean or individual values.
Jackson et al. (1997) examined adult volunteers in the United States who had lived at least 30 years in communities with natural fluoride concentrations in drinking water of 0.2, 1.0, or 4.0 mg/L. Mean values for plasma calcium, phosphate, and alkaline phosphatase for all groups were within the normal ranges, although there were statistically significant differences among groups for calcium and phosphate concentrations. On the basis of plasma fluoride concentrations, the group in the 0.2-mg/L community was thought to have higher fluoride intake than expected solely from their drinking water. Calcium intakes and general nutritional status were not discussed, and PTH concentrations were not measured.

**Human Studies (Endemic Skeletal Fluorosis)**

Six papers (five from India and one from South Africa) describe parathyroid function in cases of endemic skeletal fluorosis (see Appendix E, Table E-13). An additional paper describes a U.S. patient with renal insufficiency, systemic fluorosis attributed to the renal insufficiency (and resulting polydipsia), and serum immunoreactive PTH more than three times the normal value (Juncos and Donadio 1972). The patient’s fluoride intake at the time of the study was about 20 mg/day, or 0.34 mg/kg/day. Johnson et al. (1979) refer to that patient and 5 others with renal disease in whom fluoride (approximately 1.7-3 mg/L in drinking water) “may have been the cause of detectable clinical and roentgenographic effects.” They state that plasma PTH concentrations were elevated in all 6, albeit the concentrations were considered “relatively low” for the severity of the bone disease. Two other U.S. patients with skeletal fluorosis but no renal disease did not have elevated PTH concentrations (Felsenfeld and Roberts 1991; Whyte et al. 2005).

Singh et al. (1966) found significantly higher serum alkaline phosphatase values in individuals with fluorosis but no significant differences between patients and controls in serum calcium or inorganic phosphate. They did not measure PTH.

Teotia and Teotia (1973) reported that 5 of 20 patients with skeletal fluorosis had clear evidence of secondary hyperparathyroidism. The estimated mean fluoride intake was >25 mg/day; dietary calcium and vitamin D were considered adequate. Laboratory results showed increased plasma alkaline phosphatase, increased phosphate clearance, decreased tubular reabsorption of phosphate, increased urinary fluoride, and decreased urinary calcium. Plasma calcium and phosphate were normal in four of the patients. Elevated serum immunoreactive parathyroid hormone was observed in all five, especially in the person with elevated plasma calcium and decreased plasma phosphate. This person, who was thought to have been developing tertiary hyperparathyroidism, was later found to have a parathyroid
adenoma. Radiological findings in all five people were consistent with hyperparathyroidism.

Teotia et al. (1978) reported increased PTH concentrations in four of seven patients with endemic skeletal fluorosis (including the patient with the lowest fluoride intake); increased alkaline phosphatase was seen in at least three, and increased calcitonin was seen in all seven (Figure 8-3; Table E-10). Radiographs of two persons were consistent with secondary hyperparathyroidism. Dietary intakes of fluoride were estimated to range from 8.7 to 52 mg/day. Plasma calcium concentrations in the fluorosis patients were generally in the normal range, but urinary calcium concentrations were lower than those of controls; dietary calcium intakes were considered to be adequate. Vitamin D deficiency was not found. The finding that not everyone had elevated PTH is consistent with other observations of variability in individual responses.

Srivastava et al. (1989) described four siblings in India with skeletal fluorosis, normal total and ionized calcium concentrations, and normal vitamin D concentrations. The mother of the four had subnormal total and ionized calcium and subnormal vitamin D. All five individuals had significantly elevated PTH, elevated osteocalcin, and elevated alkaline phosphatase (Figure 8-4). Fluoride intakes were estimated to be between 16 and 49

![Graph](http://www.nap.edu/catalog/11571.html)

**FIGURE 8-3** Plasma immunoreactive parathyroid hormone (IPTH) versus fluoride intake for nine skeletal fluorosis patients (two of whom had moved to a low-fluoride area) and five controls (data from Teotia et al. 1978; see Appendix E, Tables E-10 and E-13). Note that two of the control patients shown with IPTH values of 0.35 µg/mL were actually reported as “< 0.35” µg/mL. The four IPTH values of 0.7 µg/mL or greater were considered elevated above the values found in healthy controls.
Fluoride intake and serum fluoride (upper left) in four Indian siblings (subjects 2-5) and their mother (subject 1). Serum PTH and osteocalcin and plasma alkaline phosphatase are shown for the same subjects and for normal age-matched Indian controls. SOURCE: Srivastava et al. 1989.

Pettifor et al. (1989) described a study of 260 children between 6 and 16 years old in an area of South Africa with endemic skeletal fluorosis (water fluoride concentrations of 8-12 mg/L). Hypocalcemia was present in 23% of these children and in six of nine children presenting with skel-
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etal symptoms who were studied individually. In comparable areas with low fluoride concentrations, the prevalence of hypocalcemia was only 2% to 13%. Bone fluoride was elevated about 10-fold in the seven children measured. The children exhibited a reduced phosphaturic response during a PTH-stimulation test, suggestive of pseudohypoparathyroidism Type II; the response was directly related to the presence of hypocalcemia and could be corrected by correcting the hypocalcemia. Biopsies of iliac crest bone gave a picture of severe hyperosteooidosis associated with secondary hyperparathyroidism and a mineralization defect. The authors suggested that fluoride ingestion might increase calcium requirements and exacerbate the prevalence of hypocalcemia. The usual result of low calcium intake is classical rickets and generalized osteopenia; in this case, the combination of low calcium and high fluoride resulted in a different presentation at a later age. The degree of hypocalcemia appears to play a major role in determining the severity of osteomalacia present in endemic skeletal fluorosis and influences the renal response to hyperparathyroidism (in terms of variable serum phosphate values). The authors also pointed out the “striking male predominance” of skeletal fluorosis in their study and cited similar findings in previous studies.

Gupta et al. (2001) described a one-time study of children aged 6-12 in four regions of India with different fluoride intakes (for details, see Appendix E, Table E-14). Mean serum calcium concentrations were within the normal range for all groups. The serum PTH in all groups was correlated with the fluoride intake (Figure 8-5) and with the severity of clinical and skeletal fluorosis. The authors concluded that the increased serum PTH was related to high fluoride ingestion and could be responsible for maintaining serum calcium concentrations as well as playing a role in the toxic manifestations of fluorosis. Calcium intake is not stated in the paper, but the primary author has indicated that calcium intake in the study areas was normal (S. K. Gupta, Satellite Hospital, Banipark, Jaipur, personal communication, December 11, 2003).

In a review of skeletal fluorosis, Krishnamachari (1986) indicated that the nature (osteosclerotic, osteomalacic, osteoporotic) and severity of the fluorosis depend on factors such as age, sex, dietary calcium intake, dose and duration of fluoride intake, and renal efficiency in fluoride handling. In some cases, secondary hyperparathyroidism is observed with associated characteristic bone changes. He also noted the preponderance of males among fluorosis patients and discussed a possible protective effect of estrogens. In his review, Krishnamachari (1986) described a twofold model for the body’s handling of fluoride.

1. In the presence of adequate calcium, absorbed fluoride is deposited in the bone as calcium fluorapatite. Bone density increases, urinary fluoride
FIGURE 8-5  Parathyroid hormone (IPTH) versus fluoride intake for children in four villages with different mean fluoride intakes (Gupta et al. 2001; also see Appendix E, Tables E-13 and E-14). Vertical lines indicate standard deviations on the means. Horizontal lines indicate normal range of IPTH (48.1 ± 11.9 pM/L) for this method of measurement.

Increases, but urinary calcium and phosphorus are not altered. Osteosclerosis and calcification of many tendons and ligaments occur. Serum alkaline phosphatase activity is elevated, but no specific changes occur in other constituents of serum. There are minimal hormonal changes and only mild secondary hyperparathyroidism. If the situation progresses, there will be osteophytosis (bony outgrowths), neurological complications,\(^8\) and late crippling, producing an osteosclerotic form of fluorosis that primarily affects adults.

2. In the presence of inadequate calcium, fluoride directly or indirectly stimulates the parathyroid glands, causing secondary hyperparathyroidism leading to bone loss. Bone density is variably increased, with areas of sclerosis or porosis; there is evidence (radiological and densitometrical) of bone loss. There is renal conservation of calcium in spite of hyperparathyroidism, with no significant changes in serum biochemistry; urinary hydroxyproline excretion is significantly increased. In these conditions, an osteoporotic type of skeletal fluorosis occurs at a younger age, and growing children develop deformities due to bone softening.

\(^8\)“Neurological complications” probably refers to the effects of compression of the spinal cord, e.g., those described by Singh et al. (1961).
Teotia et al. (1998) compared a number of epidemiologic studies of skeletal fluorosis from 1963 to 1997, including 45,725 children consuming water with fluoride at 1.5-25 mg/L. They observed that the combination of fluoride exposure and calcium deficiency led to more severe effects of fluoride, metabolic bone diseases, and bone deformities, resulting from excess fluoride, low calcium, high PTH, and high 1,25-dihydroxy vitamin D3. Fluoride exposure in the presence of calcium sufficiency led to an osteosclerotic form of fluorosis, with minimal secondary hyperparathyroidism. For comparable fluoride intake, metabolic bone disease occurs in 90% of children with calcium deficiency versus 25% of children with adequate calcium intake. The authors concluded that the toxic effects of fluoride occur at a lower fluoride intake (>2.5 mg/day) when there is a calcium deficiency and that fluoride appears to exaggerate the metabolic effects of calcium deficiency on bone.

Discussion (Parathyroid Function)

Of the animal studies that actually measured PTH, two studies have shown no effect of fluoride on PTH concentrations in blood (Liu and Baylink 1977; Andersen et al. 1986); animals in these studies were supplied with adequate or high dietary calcium. An additional three studies reported no effect of fluoride on serum or plasma calcium concentrations but did not measure PTH concentrations (Rosenquist and Boquist 1973; Dunipace et al. 1995, 1998). Rosenquist and Boquist (1973) gave no information on dietary calcium. One experiment by Dunipace et al. (1998) specifically used low dietary calcium for some treatment groups. Turner et al. (1997) found decreased serum calcium and elevated (but not significantly so) PTH in fluoride-treated animals with high dietary calcium. Both Verma and Guna Sherlin (2002b) and Tiwari et al. (2004) reported hypocalcemia due to combined calcium deficiency and fluoride exposure, but PTH was not measured. Tiwari et al. (2004) described changes in gene expression that would result in reduced calcium absorption from the gut. Elevated PTH concentrations were reported for fluoride-treated animals in three papers, including one with no information on dietary calcium (Faccini and Care 1965), one with normal dietary calcium and decreased serum calcium (Chavassieux et al. 1991), and one with low dietary calcium (Li and Ren 1997). In one other study, the normal response to a calcium deficiency (elevated PTH) did not occur in fluoride-exposed animals (Rosenquist et al. 1983).

Human studies show elevated PTH concentrations in at least some individuals at doses of 0.4-0.6 mg/kg/day (Teotia and Teotia 1973; Larsen et al. 1978; Duursma et al. 1987; Dandona et al. 1988; Stamp et al. 1988, 1990; Srivastava et al. 1989; Dure-Smith et al. 1996; Gupta et al. 2001) and in some cases at doses as low as 0.15 mg/kg/day (Teotia et al. 1978).
and 0.34 mg/kg/day (Juncos and Donadio 1972). Li et al. (1995) found a significant decrease in mean plasma calcium concentrations with increased fluoride exposure in populations of apparently healthy adults with inadequate nutrition, but PTH was not measured. Jackson et al. (1994) found calcium concentrations outside the normal range in 2 of 25 persons treated with fluoride for osteoporosis, but the mean value for the group was within the normal range; these persons also received calcium supplementation. Calcium concentrations in 24 patients decreased from pretreatment concentrations; however, PTH concentrations were not measured. Jackson et al. (1997) also found no significant effect of fluoride on blood calcium concentrations in people who lived in communities with different fluoride concentrations but presumably had adequate nutrition; PTH concentrations were not measured.

The indirect action of fluoride on parathyroid function is relatively straightforward: fluoride induces a net increase in bone formation (Chavassieux et al. 1991) and also decreases calcium absorption from the gastrointestinal tract (beyond the degree expected by formation of calcium-fluoride complexes; Krishnamachari 1986; Stamp et al. 1988; EKambaran and Paul 2001); both of these effects lead to an increase in the body’s calcium requirement (Petifor et al. 1989; EKambaran and Paul 2001). If dietary calcium is inadequate to support the increased requirement, the response is an increase in PTH (secondary hyperparathyroidism). PTH acts to increase resorption of bone, but the effect is uneven; low-fluoride bone is resorbed first (Faccini 1969). As bone fluoride increases, the “solubility” of the bone, or the ease with which it is resorbed, is decreased (because of the greater stability of fluorapatite), giving an apparent resistance to the effects of PTH (Faccini 1969; Levy et al. 1970; Messer et al. 1973a,b). The indirect action of fluoride to cause an increased calcium requirement is consistent with reports of reduced milk production (due to inadequate mobilization of calcium from bone) in livestock with excessive fluoride consumption and of more severe fluorosis in lactating animals (due to the higher calcium utilization during lactation) (e.g., Eckerlin et al. 1986a,b; Jubb et al. 1993). The work of Tiwari et al. (2004) provides an initial description of a mechanism by which fluoride exposure in the presence of a calcium deficiency further increases the dietary requirement for calcium, namely by altering the expression of genes necessary for calcium absorption from the gastrointestinal tract.

Some studies also indicate direct effects of fluoride on the parathyroid gland. Elevated PTH in the presence of normal serum calcium might indicate a stimulatory effect of fluoride (Gill et al. 1989; Srivastava et al. 1989). The absence of the normal elevation of PTH in response to calcium deficiency suggests an inhibitory effect (Rosenquist et al. 1983), as do several in vitro studies (Chen et al. 1988; Shoback and McGhee 1988; Sugimoto et al. 1990; Ridefelt et al. 1992). The possibility also exists that a direct effect on either
the parathyroid or the thyroid parafollicular cells leads to a compensatory response from the other, but this has not been examined.

Several studies have reported different responses among individuals or variability in group responses (Teotia and Teotia 1973; Teotia et al. 1978; Krishnamachari 1986; Duursma et al. 1987; Dandona et al. 1988; Stamp et al. 1988; 1990; Jackson et al. 1994; Dure-Smith et al. 1996; Gupta et al. 2001); the reasons for these differences are not clear but might include genetic differences in addition to variability in nutritional factors. The effects also might vary with age, sex, and the duration (as well as degree) of hypocalcemia.

Any cause of hypocalcemia or vitamin D deficiency can lead to secondary hyperparathyroidism (elevated PTH) in an attempt by the body to maintain calcium homeostasis (Ahmad and Hammond 2004). Fluoride clearly has the effect of decreasing serum calcium and increasing the calcium requirement in some or many exposed persons. In those studies which have measured it, PTH is elevated in some persons in response to fluoride exposure, indicating secondary hyperparathyroidism. No information has been reported in those studies on the clinical effects, if any, in those persons. In general, secondary hyperparathyroidism in response to calcium deficiency may contribute to a number of diseases, including osteoporosis, hypertension, arteriosclerosis, degenerative neurological diseases, diabetes mellitus, some forms of muscular dystrophy, and colorectal carcinoma (Fujita and Palmieri 2000). McCarty and Thomas (2003) suggest that down-regulation of PTH (by calcium and/or vitamin D supplementation) could assist in control of weight and prevention of diabetes.

Calcium deficiency induced or exacerbated by fluoride exposure may contribute to other adverse health effects. For example, Goyer (1995) indicates that low dietary calcium increases the concentration of lead in critical organs and the consequent toxicity. A recent increase in the number of cases of nutritional rickets in the United States appears to reflect calcium-deficient diets rather than vitamin D deficiencies (DeLucia et al. 2003). These cases occur in children whose diet lacks dairy products; circulating PTH concentrations are elevated, as are alkaline phosphatase concentrations. The authors “emphasize that nutritional calcium deficiency may occur in North American infants and is not limited to the setting of developing countries” and state that “factors that affect calcium absorption may be important in determining a susceptibility to the development of rickets.”

9 Renal failure is the most common cause of secondary hyperparathyroidism (Ahmad and Hammond 2004).

10 A diet low in dairy products will have not only a lower calcium content but probably also a higher fluoride content, due to greater use of beverages such as juices that have been manufactured with fluoridated municipal water (see Chapter 2); absorption and retention of fluoride will be higher because of the calcium deficiency.
PINEAL GLAND

The pineal gland is a small organ (150 mg in humans) located near the center of the brain. One of the major components of the mammalian circadian system, it lies in the upper margins of the thalamus in the dorsal aspects of the third ventricle and has both physical and neuronal connections with the brain. Although the pineal gland lies outside the blood-brain barrier, it has access to the cerebrospinal fluid. The pineal gland’s major neuronal connections with the brain are the sympathetic nerve fibers coming from the superior cervical ganglion; the activity of these sympathetic nerves controls synthesis and release of the pineal hormone melatonin (Cone et al. 2002).\textsuperscript{11} Other substances (primarily peptides) are also secreted from the pineal gland and have been reported to have various physiological effects, including antigonadotropic, metabolic, and antitumor activity (Anisimov 2003).

Most melatonin production occurs during darkness (Reiter 1998; Salti et al. 2000; Cone et al. 2002; Murcia García et al. 2002). Peak serum concentrations of melatonin occur during childhood in humans, with decreasing concentrations during adolescence before stabilization at the low concentration characteristic of adults (García-Patterson et al. 1996; Murcia García et al. 2002); further decreases in melatonin occur at menopause in women and at a corresponding age in men (Reiter 1998).

Melatonin affects target tissues, such as the hypophyseal pars tuberalis, that have a high density of melatonin receptors. The primary effect seems to be temporally specific activation of cAMP-sensitive gene expression in the pars tuberalis by the sensitization of adenyl cyclase, thus synchronizing the suprachiasmatic nucleus of the hypothalamus and clock-controlled genes in peripheral tissue (Stehle et al. 2003). In humans, changes in melatonin are associated with the status of the reproductive system—onset of puberty, stage of puberty, menstrual cyclicity, menopause (Reiter 1998; Salti et al. 2000)—but the functional relationships are not fully understood. The elevated melatonin concentrations characteristic of prepubertal age suggest an inhibitory effect on pubertal development (Aleandri et al. 1997; Salti et al. 2000); sexual maturation begins when serum melatonin starts to decrease (Aleandri et al. 1997; Reiter 1998). Melatonin also seems to be involved with anxiety reactions; for example, the beneficial effects of fluoxetine (Prozac) in mice during an anxiety test are not found if the pineal gland has been removed (Uz et al. 2004).

Melatonin and pineal peptides have been associated with a number of other physiological effects, including regulation of circadian rhythms and

\textsuperscript{11}Melatonin is also found in cells lining the gut from stomach to colon. Its functions are mainly protective, including free radical scavenging. Some of melatonin’s actions are receptor-mediated and involve the central and peripheral sympathetic nervous systems (Reiter et al. 2003a).
EFFECTS ON THE ENDOCRINE SYSTEM

sleep (Arendt 2003; Cajochen et al. 2003); regulation of reproductive physiology in seasonal breeders (Aleandri et al. 1997; Reiter 1998; Stehle et al. 2003); effects on calcium and phosphorus metabolism, parathyroid activity, bone growth, and development of postmenopausal osteoporosis (Chen et al. 1990, 1991; Sandyk et al. 1992; Shoumura et al. 1992; el-Hajj Fuleihan et al. 1997; Roth et al. 1999; Cardinali et al. 2003; Goodman 2003); oncostatic or anticarcinogenic effects (Cohen et al. 1978; García-Patterson et al. 1996; Panzer 1997; Anisimov 2003); antioxidant actions (Srinivasan 2002; Reiter et al. 2003b); and effects on the central nervous system, psychiatric disease, and sudden infant death syndrome (García-Patterson et al. 1996; Reiter 1998; Delagrange et al. 2003). Panzer (1997) suggested that the simultaneous decrease in melatonin concentrations and the exponential increase in bone growth during puberty could be a factor in the typical age distribution of osteosarcoma.

Pineal Gland Calcification

The pineal gland is a calcifying tissue; in humans, calcified concretions can be found at any age, although the likelihood increases with age (Vígh et al. 1998; Akano and Bickler 2003) and may be associated with menopause (Sandyk et al. 1992). The occurrence of pineal calcifications varies among different populations and nations (Vígh et al. 1998), possibly in association with the degree of industrialization (Akano and Bickler 2003), rates of breast cancer (Cohen et al. 1978), and high circannual light intensity near the equator (Vígh et al. 1998). Osteoporosis might be associated with fewer concretions (Vígh et al. 1998).

Melatonin secretion is well correlated with the amount of uncalcified pineal tissue (Kunz et al. 1999) but not with the size of pineal calcification (Vígh et al. 1998; Kunz et al. 1999). An increase in calcification of the pineal gland in humans probably represents a decrease in the number of functioning pinealocytes and a corresponding decrease in the individual’s ability to produce melatonin (Kunz et al. 1999). The degree of calcification, relative to the size of an individual’s pineal gland, has been suggested as a marker of the individual’s decreased capability to produce melatonin (Kunz et al. 1999).

As with other calcifying tissues, the pineal gland can accumulate fluoride (Luke 1997, 2001). Fluoride has been shown to be present in the pineal glands of older people (14-875 mg of fluoride per kg of gland in persons aged 72-100 years), with the fluoride concentrations being positively related to the calcium concentrations in the pineal gland, but not to the bone fluoride, suggesting that pineal fluoride is not necessarily a function of cumulative fluoride exposure of the individual (Luke 1997, 2001). Fluoride has not been measured in the pineal glands of children or young adults, nor
has there been any investigation of the relationship between pineal fluoride concentrations and either recent or cumulative fluoride intakes.

**In Vitro Studies**

Few studies have examined the effects of fluoride on pineal function. NaF (2.5-20 mM, or fluoride at 47.5-380 mg/L) produces markedly increased adenylyl cyclase activity (up to four times control activity) of rat pineal homogenates in vitro (Weiss 1969a,b), as it does in other tissues (Weiss 1969a); ATPase activity in the homogenates was inhibited by up to 50% (Weiss 1969a). Potassium fluoride (7-10 mM, or fluoride at 133-190 mg/L) has been used experimentally to increase adenylyl cyclase activity in rat pineal glands in vitro (Zatz 1977, 1979).

**Animal Studies**

Details of the effect of fluoride on pineal function are presented in Appendix E, Table E-15. Luke (1997) examined melatonin production as a function of age and time of day in Mongolian gerbils (*Meriones unguiculatus*). On an absolute basis, melatonin production by the low-fluoride group was constant at ages 7-28 weeks, with no difference between males and females. Relative to body weight, melatonin output declined progressively with age until adulthood (by 11.5 weeks in females and 16 weeks in males). In contrast, prepubescent gerbils fed the high-fluoride diet had significantly lower pineal melatonin production than prepubescent gerbils fed the low-fluoride diet. Relative to body weight, the normal higher rate of melatonin production in sexually immature gerbils did not occur.

Sexual maturation in females occurred earlier in the high-fluoride animals (Luke 1997); males had increases in melatonin production relative to body weight between 11.5 and 16 weeks (when a decrease normally would occur), and testicular weight at 16 weeks (but not at 9 or 28 weeks) was significantly lower in high-fluoride than in low-fluoride animals. The circadian rhythm of melatonin production was altered in the high-fluoride animals at 11.5 weeks but not at 16 weeks. In high-fluoride females at 11.5 weeks, the nocturnal peak (relative to body weight) occurred earlier than in the low-fluoride animals; also, the peak value was lower (but not significantly lower) in the high-fluoride animals. In males, a substantial reduction ($P < 0.00001$) in the nocturnal peak (relative to body weight) was observed in the high-fluoride animals.
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Human Studies

Although no studies are available that specifically address the effect of fluoride exposure on pineal function or melatonin production in humans, two studies have examined the age of onset of menstruation (age of menarche) in girls in fluoridated areas (Schlesinger et al. 1956; Farkas et al. 1983; for details, see Appendix E, Table E-15); the earlier study was discussed by Luke (1997) as part of the basis for her research. No comparable information on sexual maturation in boys is available.

In girls examined approximately 10 years after the onset of fluoridation (1.2 mg/L, in 1945) in Newburgh, New York, the average age at menarche was 12 years, versus 12 years 5 months among girls in unfluoridated Kingston (Schlesinger et al. 1956). The authors stated that this difference was not statistically significant. Note that those girls who reached menarche during the time period of the study had not been exposed to fluoride over their entire lives, and some had been exposed perhaps for only a few years before menarche (they would have been 8-9 years old at the time fluoridation was started). Those girls in Newburgh who had been exposed to fluoridated water since birth (or before birth) had not yet reached menarche by the time of the study.

A later study in Hungary (Farkas et al. 1983) reported no difference in the menarcheal age of girls in a town with “optimal” fluoride concentration (1.09 mg/L in Kunszentmárton, median menarcheal age 12.779 years) and a similar control town (0.17 mg/L in Kiskunmajsa; median menarcheal

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12Both Schlesinger et al. (1956) and Farkas et al. (1983) referred to tables of the distribution of ages at the time of first menstruation, but, in fact, both studies provided only frequencies by age (presumably at the time of study, in either 1-year or 0.5-year increments) of girls having achieved menarche by the stated age. Farkas et al. (1983) specifically indicated use of the probit method for ascertainment of the median age at menarche; the data provided by Schlesinger et al. (1956) appear to correspond to that method, but they do not specifically mention it. The probit (or status quo) method appears to be routinely used to estimate the median (or other percentiles of) age at menarche, sometimes in conjunction with an estimated mean age at menarche based on recall data (e.g., Wu et al. 2002; Anderson et al. 2003; Chumlea et al. 2003; Padez and Rocha 2003). According to Grumbach and Styne (2002), “The method of ascertainment of the age of menarche is of importance. Contemporaneous recordings are performed with the probit method of asking, ‘yes’ or ‘no,’ are you menstruating? These may be incorrect because of social pressures of the culture and socioeconomic group considered. Recalled ages of menarche are used in other studies and considered to be accurate within 1 year (in 90% of cases) during the teenage years and in older women, too.”

13 Probably the median age, although the text simply says “average.” Similar studies appear to use the term “average age at menarche” to refer to the “estimated median age at menarche” (Anderson et al. 2003).

14 For comparison purposes, estimates of mean or median age at menarche for the white population in the United States include 12.80 years for 1963-1970 (Anderson et al. 2003) and 12.55-12.7 years for 1988-1994 (Wu et al. 2002; Anderson et al. 2003; Chumlea et al. 2003).
age 12.79 years). This study shows postmenarcheal girls present at younger ages in the higher fluoride town than in the low-fluoride town, although the reported median ages were the same (Farkas et al. 1983).

Discussion (Pineal Function)

Whether fluoride exposure causes decreased nocturnal melatonin production or altered circadian rhythm of melatonin production in humans has not been investigated. As described above, fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans. Actual effects in any individual depend on age, sex, and probably other factors, although at present the mechanisms are not fully understood.

OTHER ENDOCRINE ORGANS

The effects of fluoride exposure have been examined for several other endocrine organs, including the adrenals, the pancreas, and the pituitary (for details, see Appendix E, Tables E-16 and E-17). Effects observed in animals include changes in organ weight, morphological changes in tissues, increased mitotic activity, decreased concentrations of pituitary hormones, depressed glucose utilization, elevated serum glucose, and elevated insulin-like growth factor-1 (IGF-1). Effects reported in humans include “endocrine disturbances,” impaired glucose tolerance, and elevated concentrations of pituitary hormones. Studies of the effects of fluoride on glucose metabolism and in diabetic animals are discussed below; information on other effects is extremely limited.

Animal Studies (Diabetic Animals)

Two studies have examined the effects of fluoride exposure in diabetic rats. In the first study, Dunipace et al. (1996) compared male Zucker fatty diabetic rats and Zucker age-matched controls given drinking water with fluoride at 5, 15, or 50 mg/L. For the physiological, biochemical, and genetic variables that were monitored, no “measurable adverse effects” were noted. Statistically significant differences with respect to fluoride intake (as opposed to differences between normal and diabetic animals) were observed only for diabetic rats with fluoride at 50 mg/L. No endocrinological parameters (e.g., PTH) were measured. Dunipace et al. (1996) reported that fluoride intake, excretion, and balance were generally similar in this study and

\[15\] These fluoride intakes were considered to be equivalent to intakes by humans of 1, 3, and 10 mg/L (Dunipace et al. 1996).
in a previous study with Sprague-Dawley rats but that there were “strain-specific differences in fluoride sensitivity”; these differences were not defined or explained. The Zucker fatty diabetic rat is considered to be an animal model for human Type II (noninsulin-dependent) diabetes mellitus, although the diabetic rats in this study did not experience renal insufficiency, and the study was terminated before an age that might be more comparable to ages associated with late-onset diabetes and diabetic complications in humans. The authors concluded that the diabetic rats “were not at increased risk of fluorosis,” even though femoral fluoride concentrations (2,700-9,500 µg/g in ash for diabetic rats given fluoride at 15 or 50 mg/L versus 2,500-3,600 in normal rats given fluoride at 50 mg/L) were in the range associated with fluorosis in humans and exceeded concentrations of bone fluoride associated with decreased bone strength in rabbits (6,500-8,000 ppm in ash; Turner et al. 1997); no basis for their conclusion was given.

In the second study, Boros et al. (1998) compared the effects of fluoride at 10 mg/L in drinking water for 3 weeks on young female rats (Charles River, Wistar), either normal (nondiabetic) or with streptozotocin-induced, untreated diabetes. An additional group of normal rats was given an amount of fluoride in drinking water corresponding to the fluoride intake by the diabetic rats (up to about 3 mg/day per rat). Both feed and water consumption increased significantly in the diabetic rats (with and without fluoridated water); water consumption was significantly higher in the diabetic rats on fluoridated water than in those on nonfluoridated water. Fasting blood glucose concentrations were increased significantly in both diabetic groups, but more so in the group on fluoridated water. Fluoride treatment of nondiabetic animals did not cause any significant alteration in blood glucose concentrations. Plasma fluoride was higher, and bone fluoride was lower, in diabetic than in nondiabetic animals given the same amount of fluoride, indicating lower deposition of fluoride into bone and lower renal clearance of fluoride in the diabetic animals. The increased kidney weight found in diabetic animals on nonfluoridated water was not seen in the fluoride-treated diabetic animals. Additional biochemical and hormonal parameters were not measured.

In contrast to the Zucker fatty diabetic rats in the study by Dunipace et al. (1996), the streptozotocin-induced diabetic rats in this study (Boros et al., 1998) provide an animal model considered representative of Type I (insulin-dependent) diabetes mellitus in humans. In these rats, the general severity of the diabetes (blood glucose concentrations, kidney function, weight loss) was worse in animals given fluoride at 10 mg/L in their drinking water. In both types of diabetic rats, fluoride intake was very high because of the several-fold increase in water consumption, and corresponding plasma, soft tissue, and bone fluoride concentrations were elevated accordingly. Thus, any health effects related to plasma or bone fluoride...
concentrations, for example, would be expected to occur in animals or humans with uncontrolled (or inadequately controlled) diabetes at lower fluoride concentrations in drinking water than for nondiabetics, because of the elevated water intakes. In addition, the results reported by Boros et al. (1998) suggested that, for some situations (e.g., diabetes in which kidney function is compromised), the severity of the diabetes could be increased with increasing fluoride exposure.

Animal Studies (Normal Animals)

Turner et al. (1997) reported a 17% increase in serum glucose in female rabbits given fluoride in drinking water at 100 mg/L for 6 months. IGF-1 was also significantly increased (40%) in these rabbits, but other regulators of serum glucose, such as insulin, were not measured. The authors suggested that IGF-1 concentrations might have changed in response to changes in serum glucose concentrations. Dunipace et al. (1995, 1998) found no significant differences with chronic fluoride treatment in mean blood glucose concentrations in rats; specific data by treatment group were not reported, and parameters such as insulin and IGF-1 were not measured.

Suketa et al. (1985) and Grucka-Mamczar et al. (2005) have reported increases in blood glucose concentrations following intraperitoneal injections of NaF; Suketa et al. (1985) attributed these increases to fluoride stimulation of adrenal function. Rigalli et al. (1990, 1992, 1995), in experiments with rats, reported decreases in insulin, increases in plasma glucose, and disturbance of glucose tolerance associated with increased plasma fluoride concentrations. The effect of high plasma fluoride (0.1-0.3 mg/L) appeared to be transient, and the decreased response to a glucose challenge occurred only when fluoride was administered before (as opposed to together with or immediately after) the glucose administration (Rigalli et al. 1990). In chronic exposures, effects on glucose metabolism occurred when plasma fluoride concentrations exceeded 0.1 mg/L (5 µmol/L) (Rigalli et al. 1992, 1995). The in vivo effect appeared to be one of inhibition of insulin secretion rather than one of insulin-receptor interaction (Rigalli et al. 1990). Insulin secretion (both basal and glucose-stimulated) by isolated islets of Langerhans in vitro was also inhibited as a function of fluoride concentrations (Rigalli et al. 1990, 1995). Rigalli et al. (1990) pointed out that recommended plasma fluoride concentrations for treatment of osteoporosis are similar to those shown to affect insulin secretion.

Human Studies

Jackson et al. (1994) reported no differences in mean fasting blood glucose concentrations between osteoporosis patients treated with fluoride and
untreated controls, although 3 of 25 treated individuals had values outside the normal range (versus 1 of 38 controls). No significant differences were found between groups of older adults with different fluoride concentrations in drinking water in studies in China (Li et al. 1995; subjects described as “healthy” adults) and the United States (Jackson et al. 1997), and all mean values were within normal ranges. Glucose tolerance tests were not conducted in these studies.

Trivedi et al. (1993) reported impaired glucose tolerance in 40% of young adults with endemic fluorosis, with fasting serum glucose concentrations related to serum fluoride concentrations; the impaired glucose tolerance was reversed after 6 months of drinking water with “acceptable” fluoride concentrations (<1 mg/L). It is not clear whether individuals with elevated serum fluoride and impaired glucose tolerance had the highest fluoride intakes of the group with endemic fluorosis or a greater susceptibility than the others to the effects of fluoride. For all 25 endemic fluorosis patients examined, a significant positive correlation between serum fluoride and fasting serum immunoreactive insulin (IRI) was observed, along with a significant negative correlation between serum fluoride and fasting glucose/insulin ratio (Trivedi et al. 1993).

The finding of increased IRI contrasts with findings of decreased insulin in humans after exposure to fluoride (Rigalli et al. 1990; de la Sota et al. 1997) and inhibition of insulin secretion by rats, both in vivo and in vitro (Rigalli et al. 1990, 1995). However, the assay for IRI used by Trivedi et al. (1993) could not distinguish between insulin and proinsulin, and the authors suggested that the observed increases in both IRI and serum glucose indicate either biologically inactive insulin—perhaps elevated proinsulin—or insulin resistance. Inhibition of one of the prohormone convertases (the enzymes that convert proinsulin to insulin) would result in both elevated proinsulin secretion and increased blood glucose concentrations and would be consistent with the decreased insulin secretion reported by Rigalli et al. (1990, 1995) and de la Sota et al. (1997). Although Turner et al. (1997) suggested fluoride inhibition of insulin-receptor activity as a mechanism for increased blood glucose concentrations, Rigalli et al. (1990) found no difference in response to exogenous insulin in fluoride-treated versus control rats, consistent with no interference of fluoride with the insulin-receptor interaction.

Discussion (Other Endocrine Function)

More than one mechanism for diabetes or impaired glucose tolerance exists in humans, and a variety of responses to fluoride are in keeping with

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16In the study by Jackson et al. (1997), samples were nonfasting; in the study by Li et al. (1995), it is not clear whether samples were fasting or nonfasting.
variability among strains of experimental animals and among the human population. The conclusion from the available studies is that sufficient fluoride exposure appears to bring about increases in blood glucose or impaired glucose tolerance in some individuals and to increase the severity of some types of diabetes. In general, impaired glucose metabolism appears to be associated with serum or plasma fluoride concentrations of about 0.1 mg/L or greater in both animals and humans (Rigalli et al. 1990, 1995; Trivedi et al. 1993; de al Sota et al. 1997). In addition, diabetic individuals will often have higher than normal water intake, and consequently, will have higher than normal fluoride intake for a given concentration of fluoride in drinking water. An estimated 16-20 million people in the United States have diabetes mellitus (Brownlee et al. 2002; Buse et al. 2002; American Diabetes Association 2004; Chapter 2); therefore, any role of fluoride exposure in the development of impaired glucose metabolism or diabetes is potentially significant.

**SUMMARY**

The major endocrine effects of fluoride exposures reported in humans include elevated TSH with altered concentrations of T3 and T4, increased calcitonin activity, increased PTH activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity; similar effects have been reported in experimental animals. These effects are summarized in Tables 8-1 and 8-2, together with the approximate intakes or physiological fluoride concentrations that have been typically associated with them thus far. Table 8-2 shows that several of the effects are associated with average or typical fluoride intakes of 0.05-0.1 mg/kg/day (0.03 with iodine deficiency), others with intakes of 0.15 mg/kg/day or higher. A comparison with Chapter 2 (Tables 2-13, 2-14, and 2-15) will show that the 0.03-0.1 mg/kg/day range will be reached by persons with average exposures at fluoride concentrations of 1-4 mg/L in drinking water, especially the children. The highest intakes (>0.1 mg/kg/d) will be reached by some individuals with high water intakes at 1 mg/L and by many or most individuals with high water intakes at 4 mg/L, as well as by young children with average exposures at 2 or 4 mg/L.

Most of the studies cited in this chapter were designed to ascertain whether certain effects occurred (or in cases of skeletal fluorosis, to see what endocrine disturbances might be associated), not to determine the lowest exposures at which they do occur or could occur. Estimates of exposure listed in these tables and in Appendix E are, in most cases, estimates of average values for groups based on assumptions about body weight and water intake. Thus, individual responses could occur at lower or higher exposures than those listed. Although the comparisons are incomplete, similar effects
TABLE 8-1 Summary of Major Observed Endocrine Effects of Fluoride in Experimental Animals, with Typical Associated Intakes and Physiological Fluoride Concentrations

<table>
<thead>
<tr>
<th>End Point</th>
<th>Fluoride Intake, mg/kg/day</th>
<th>Fluoride in Serum or Plasma, mg/L</th>
<th>Fluoride in Urine, mg/L</th>
<th>Fluoride in Bone, ppm in ash</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered thyroid function (altered T4 and T3 concentrations)</td>
<td>3-6 (lower with iodine deficiency)</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥6 (possibly ≥2-3)</td>
<td>≥2,400</td>
<td>Stolc and Podoba 1960; Bobek et al. 1976; Hillman et al. 1979; Guan et al. 1988; Zhao et al. 1998; Cinar and Selcuk 2005</td>
</tr>
<tr>
<td>Altered calcitonin activity</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>3,200-3,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rantanen et al. 1972</td>
</tr>
<tr>
<td>Altered melatonin production; altered timing of sexual maturity</td>
<td>3.7</td>
<td>NA</td>
<td>NA</td>
<td>2,800</td>
<td>Luke 1997</td>
</tr>
<tr>
<td>Inhibited parathyroid function</td>
<td>5.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Rosenquist et al. 1983</td>
</tr>
<tr>
<td>Increased serum glucose; increased severity of diabetes</td>
<td>7-10.5</td>
<td>0.1-0.7&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>NA</td>
<td>&gt;1,000</td>
<td>Rigalli et al. 1990, 1992, 1995; Turner et al. 1997; Boros et al. 1998</td>
</tr>
<tr>
<td>Increased parathyroid hormone concentrations, secondary hyperparathyroidism</td>
<td>9-10</td>
<td>≥ 0.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NA</td>
<td>2,700-3,200</td>
<td>Faccini and Care 1965; Chavassieux et al. 1991</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not available.
<sup>b</sup>ppm.
<sup>c</sup>Serum.
<sup>d</sup>Plasma.

are seen in humans at much lower fluoride intakes (or lower water fluoride concentrations) than in rats or mice, but at similar fluoride concentrations in blood and urine. This is in keeping with the different pharmacokinetic behavior of fluoride in rodents and in humans (Chapter 3) and with the variability in intake, especially for humans.
### TABLE 8-2 Summary of Major Observed Endocrine Effects of Fluoride in Humans, with Typical Associated Intakes and Physiological Fluoride Concentrations

<table>
<thead>
<tr>
<th>End Point</th>
<th>Fluoride Intake, mg/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fluoride in Serum or Plasma, mg/L</th>
<th>Fluoride in Urine, mg/L</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered thyroid function (altered T4 and/or T3 concentrations)</td>
<td>0.05-0.1 (0.03 with iodine deficiency)</td>
<td>≥0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.4</td>
<td>Bachinskii et al. 1985; Lin et al. 1991; Yang et al. 1994; Michael et al. 1996; Susheela et al. 2005</td>
</tr>
<tr>
<td>Elevated TSH concentrations</td>
<td>0.05-0.1 (0.03 with iodine deficiency)</td>
<td>≥0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥2</td>
<td>Bachinskii et al. 1985; Lin et al. 1991; Yang et al. 1994; Susheela et al. 2005</td>
</tr>
<tr>
<td>Elevated calcitonin concentrations</td>
<td>0.06-0.87</td>
<td>0.11-0.26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.2-18.5 mg/day</td>
<td>Teotia et al. 1978</td>
</tr>
<tr>
<td>Goiter prevalence ≥ 20%</td>
<td>0.07-0.13 (≥ 0.01 with iodine deficiency)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>Day and Powell-Jackson 1972; Desai et al. 1993; Jooste et al. 1999</td>
</tr>
<tr>
<td>Impaired glucose tolerance in some individuals</td>
<td>0.07-0.4</td>
<td>0.08&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.8</td>
<td>Rigalli et al. 1990, 1995; Trivedi et al. 1993; de la Sota 1997</td>
</tr>
<tr>
<td>Increased parathyroid hormone concentrations, secondary hyperparathyroidism, in some individuals</td>
<td>0.15-0.87</td>
<td>0.14-0.45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3-18.5 mg/day</td>
<td>Juncos and Donadio 1972; Teotia and Teotia 1973; Larsen et al. 1978; Teotia et al. 1978; Duursma et al. 1987; Dandona et al. 1988; Stamp et al. 1988, 1990; Pettifor et al. 1989; Srivastava et al. 1989; Dure-Smith et al. 1996; Gupta et al. 2001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Serum.  
<sup>b</sup>Plasma.  
<sup>c</sup>Not available.

### Thyroid Function

Fluoride exposure in humans is associated with elevated TSH concentrations, increased goiter prevalence, and altered T4 and T3 concentrations; similar effects on T4 and T3 are reported in experimental animals, but TSH has not been measured in most studies. In animals, effects on thyroid function have been reported at fluoride doses of 3-6 mg/kg/day (some effects at...
0.4-0.6 mg/kg/day) when iodine intake was adequate (Table 8-1); effects on thyroid function were more severe or occurred at lower doses when iodine intake was inadequate. In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate (Table 8-2).

Several sets of results are consistent with inhibition of deiodinase activity, but other mechanisms of action are also possible, and more than one might be operative in a given situation. In many cases, mean hormone concentrations for groups are within normal limits, but individuals may have clinically important situations. In particular, the inverse correlation between asymptomatic hypothyroidism in pregnant mothers and the IQ of the offspring (Klein et al. 2001) is a cause for concern. The recent decline in iodine intake in the United States (CDC 2002d; Larsen et al. 2002) could contribute to increased toxicity of fluoride for some individuals.

**Thyroid Parafollicular Cell Function**

Only one study has reported calcitonin concentrations in fluoride-exposed individuals. This study found elevated calcitonin in all patients with fluoride exposures above about 0.15 mg/kg/day and in one patient with a current intake of approximately 0.06 mg/kg/day (Table 8-2); these exposures corresponded to plasma fluoride concentrations of 0.11-0.26 mg/L. Results attributed to altered calcitonin activity have also been found in experimental animals at a fluoride exposure of 2 mg/kg/day (Table 8-1). It is not clear whether elevated calcitonin is a direct or indirect result of fluoride exposure, nor is it clear what the clinical significance of elevated calcitonin concentrations might be in individuals.

**Parathyroid Function**

In humans, depending on the calcium intake, elevated concentrations of PTH are routinely found at fluoride exposures of 0.4-0.6 mg/kg/day and at exposures as low as 0.15 mg/kg/day in some individuals (Table 8-2). Similar effects and exposures have been found in a variety of human studies; these studies indicate that elevated PTH and secondary hyperparathyroidism occur at fluoride intakes higher than those associated with other endocrine effects. In the single study that measured both calcitonin and PTH, all individuals with elevated PTH also had elevated calcitonin, and several individuals had elevated calcitonin without elevated PTH (Teotia et al. 1978). Elevated concentrations of PTH and secondary hyperparathyroidism have also been reported at fluoride intakes of 9-10 mg/kg/day (and as low as 0.45-2.3 mg/kg/day in one study) in experimental animals (Table 8-1). One
animal study found what appears to be inhibition of the normal parathyroid response to calcium deficiency at a fluoride intake of 5.4 mg/kg/day.

As with calcitonin, it is not clear whether altered parathyroid function is a direct or indirect result of fluoride exposure. An indirect effect of fluoride by causing an increased requirement for calcium is probable, but direct effects could occur as well. Also, although most individuals with skeletal fluorosis appear to have elevated PTH, it is not clear whether parathyroid function is affected before development of skeletal fluorosis or at lower concentrations of fluoride exposure than those associated with skeletal fluorosis. Recent U.S. reports of nutritional (calcium-deficiency) rickets associated with elevated PTH (DeLucia et al. 2003) suggest the possibility that fluoride exposure, together with increasingly calcium-deficient diets, could have an adverse impact on the health of some individuals.

**Pineal Function**

The single animal study of pineal function indicates that fluoride exposure results in altered melatonin production and altered timing of sexual maturity (Table 8-1). Whether fluoride affects pineal function in humans remains to be demonstrated. The two studies of menarcheal age in humans show the possibility of earlier menarche in some individuals exposed to fluoride, but no definitive statement can be made. Recent information on the role of the pineal organ in humans suggests that any agent that affects pineal function could affect human health in a variety of ways, including effects on sexual maturation, calcium metabolism, parathyroid function, postmenopausal osteoporosis, cancer, and psychiatric disease.

**Glucose Metabolism**

Increased serum glucose and increased severity of existing diabetes have been reported in animal studies at fluoride intakes of 7-10.5 mg/kg/day (Table 8-1). Impaired glucose tolerance in humans has been reported in separate studies at fluoride intakes of 0.07-0.4 mg/kg/day, corresponding to serum fluoride concentrations above about 0.1 mg/L. The primary mechanism appears to involve inhibition of insulin production.

**General Considerations**

The available studies of the effects of fluoride exposure on endocrine function have several limitations. In particular, many studies did not measure actual hormone concentrations, several studies did not report nutritional status (e.g., iodine or calcium intake), and, for thyroid function, other possible goitrogenic factors have not been ruled out. Most studies have too
few exposure groups, with, for example, the “high”-fluoride group in one study having lower concentrations of fluoride in drinking water than the “normal”-fluoride group in another study. In general, the human exposures are not well characterized. Nevertheless, there is consistency among the available studies in the types of effects seen in humans and animals and in the concentrations or fluoride exposures associated with the effects in humans.

For all the endocrine effects reported to occur from fluoride exposure, the variability in exposure and response among populations (or strains of an experimental animal) or within a human population requires further attention. For example, correlations between the fluoride intake or the presence or degree of fluorosis and the presence (or prevalence) or severity of other effects generally have not been examined on an individual basis, which could permit identification of individual differences in susceptibility or response. Several reports have identified subgroups within an exposed population or group, in terms of the response observed, even when group means are not statistically different.

Variability in response to fluoride exposures could be due to differences in genetic background, age, sex, nutrient intake (e.g., calcium, iodine, selenium), general dietary status, or other factors. Intake of nutrients such as calcium and iodine often is not reported in studies of fluoride effects. The effects of fluoride on thyroid function, for instance, might depend on whether iodine intake is low, adequate, or high, or whether dietary selenium is adequate. Dietary calcium affects the absorption of fluoride (Chapter 3); in addition, fluoride causes an increase in the dietary requirements for calcium, and insufficient calcium intake increases fluoride toxicity. Available information now indicates a role for aluminum in the interaction of fluoride on the second messenger system; thus, differences in aluminum exposure might explain some of the differences in response to fluoride exposures among individuals and populations.

The clinical significance of fluoride-related endocrine effects requires further attention. For example, most studies have not mentioned the clinical significance for individuals of hormone values out of the normal range, and some studies have been limited to consideration of “healthy” individuals. As discussed in the various sections of this chapter, recent work on borderline hormonal imbalances and endocrine-disrupting chemicals indicates that significant adverse health effects, or an increased risk for development of clearly adverse health outcomes, could be associated with seemingly mild imbalances or perturbations in hormone concentrations (Brucker-Davis et al. 2001). In addition, the different endocrine organs do not function entirely separately: thyroid effects (especially elevated TSH) may be associated with parathyroid effects (Stoffer et al. 1982; Paloyan Walker et al. 1997), and glucose metabolism may be affected by thyroid or parathyroid status.
Adverse effects in individuals might occur when hormone concentrations are still in the normal ranges for a population but are low or high for that individual (Brucker-Davis et al. 2001; Belchetz and Hammond 2003). Some investigators suggest that endocrine-disrupting chemicals could be associated with nonmonotonic dose-response curves (e.g., U-shaped or inverted-U-shaped curves resulting from the superimposition of multiple dose-response curves) and that a threshold for effects cannot be assumed (Bigsby et al. 1999; Brucker-Davis et al. 2001).

In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. Fluoride is therefore an endocrine disruptor in the broad sense of altering normal endocrine function or response, although probably not in the sense of mimicking a normal hormone. The mechanisms of action remain to be worked out and appear to include both direct and indirect mechanisms, for example, direct stimulation or inhibition of hormone secretion by interference with second messenger function, indirect stimulation or inhibition of hormone secretion by effects on things such as calcium balance, and inhibition of peripheral enzymes that are necessary for activation of the normal hormone.

**RECOMMENDATIONS**

- Further effort is necessary to characterize the direct and indirect mechanisms of fluoride’s action on the endocrine system and the factors that determine the response, if any, in a given individual. Such studies would address the following:
  - the in vivo effects of fluoride on second messenger function
  - the in vivo effects of fluoride on various enzymes
  - the integration of the endocrine system (both internally and with other systems such as the neurological system)
  - identification of those factors, endogenous (e.g., age, sex, genetic factors, or preexisting disease) or exogenous (e.g., dietary calcium or iodine concentrations, malnutrition), associated with increased likelihood of effects of fluoride exposures in individuals
  - consideration of the impact of multiple contaminants (e.g., fluoride and perchlorate) that affect the same endocrine system or mechanism
  - examination of effects at several time points in the same individuals to identify any transient, reversible, or adaptive responses to fluoride exposure.

- Better characterization of exposure to fluoride is needed in epidemiology studies investigating potential endocrine effects of fluoride. Important exposure aspects of such studies would include the following:
— collecting data on general dietary status and dietary factors that could influence the response, such as calcium, iodine, selenium, and aluminum intakes
— characterizing and grouping individuals by estimated (total) exposure, rather than by source of exposure, location of residence, fluoride concentration in drinking water, or other surrogates
— reporting intakes or exposures with and without normalization for body weight (e.g., mg/day and mg/kg/day), to reduce some of the uncertainty associated with comparisons of separate studies
— addressing uncertainties associated with exposure and response, including uncertainties in measurements of fluoride concentrations in bodily fluids and tissues and uncertainties in responses (e.g., hormone concentrations)
— reporting data in terms of individual correlations between intake and effect, differences in subgroups, and differences in percentages of individuals showing an effect and not just differences in group or population means.
— examining a range of exposures, with normal or control groups having very low fluoride exposures (below those associated with 1 mg/L in drinking water for humans).

• The effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States. Major areas for investigation include the following:
  — thyroid disease (especially in light of decreasing iodine intake by the U.S. population);
  — nutritional (calcium deficiency) rickets;
  — calcium metabolism (including measurements of both calcitonin and PTH);
  — pineal function (including, but not limited to, melatonin production); and
  — development of glucose intolerance and diabetes.
Effects on the Gastrointestinal, Renal, Hepatic, and Immune Systems

This chapter evaluates the effects of fluoride on the gastrointestinal system (GI), the kidney, the liver, and the immune system, focusing primarily on new data that have been generated since the earlier NRC (1993) review. Studies that involved exposures to fluoride in the range of 2-4 milligrams per liter (mg/L) are emphasized, so that the safety of the maximum-contaminant-level goal (MCLG) can be evaluated.

GI SYSTEM

Fluoride occurs in drinking water primarily as free fluoride. When ingested some fluorides combine with hydrogen ions to form hydrogen fluoride (HF), depending on the pH of the contents of the stomach (2.4% HF at pH 5; 96% HF at pH 2). HF easily crosses the gastric epithelium, and is the major form in which fluoride is absorbed from the stomach (see Chapter 3). Upon entering the interstitial fluid in the mucosa where the pH approaches neutrality, HF dissociates to release fluoride and hydrogen ions which can cause tissue damage. Whether damage occurs depends on the concentrations of these ions in the tissue. It appears that an HF concentration somewhere between 1.0 and 5.0 mmol/L (20 and 100 mg/L), applied to the stomach mucosa for at least 15 minutes, is the threshold for effects on the function and structure of the tissue (Whitford et al. 1997). Reported GI symptoms, such as nausea, may not be accompanied by visible damage to the gastric mucosa. Thus, the threshold for adverse effects (discomfort) is likely to be lower than that proposed by Whitford et al. This review is concerned primarily with the chronic ingestion of fluoride in drinking wa-
ter containing fluoride at 2-4 mg/L. Single high doses of ingested fluoride are known to elicit acute GI symptoms, such as nausea and vomiting, but whether chronic exposure to drinking water with fluoride at 4 mg/L can elicit the same symptoms has not been documented well.

The primary symptoms of GI injury are nausea, vomiting, and abdominal pain (see Table 9-1). Such symptoms have been reported in case studies (Waldbott 1956; Petraborg 1977) and in a clinical study involving double-blind tests on subjects drinking water artificially fluoridated at 1.0 mg/L (Grimbergen 1974). In the clinical study, subjects were selected whose GI symptoms appeared with the consumption of fluoridated water and disappeared when they switched to nonfluoridated water. A pharmacist prepared solutions of sodium fluoride (NaF) and sodium silicofluoride (Na$_2$SiF$_6$) so that the final fluoride ion concentrations were 1.0 mg/L. Eight bottles of water were prepared with either fluoridated water or distilled water. Patients were instructed to use one bottle at a time for 2 weeks. They were asked to record their symptoms throughout the study period. Neither patients nor the physician administering the water knew which water samples were fluoridated until after the experiments were completed. The fluoridation chemicals added to the water at the time of the experiments were likely the best candidates to produce these symptoms. Despite those well-documented case reports, the authors did not estimate what percentage of the population might have GI problems. The authors could have been examining a group of patients whose GI tracts were particularly hypersensitive. The possibility that a small percentage of the population reacts systemically to fluoride, perhaps through changes in the immune system, cannot be ruled out (see section on the immune system later in this chapter).

Perhaps it is safe to say that less than 1% of the population complains of GI symptoms after fluoridation is initiated (Feltman and Kosel 1961). The numerous fluoridation studies in the past failed to rigorously test for changes in GI symptoms and there are no studies on drinking water containing fluoride at 4 mg/L in which GI symptoms were carefully documented. Nevertheless, there are reports of areas in the United States where the drinking water contains fluoride at concentrations greater than 4 mg/L and as much as 8 mg/L (Leone et al. 1955b). Symptoms of GI distress or discomfort were not reported. In the United Kingdom, where tea drinking is more common, people can consume up to 9 mg of fluoride a day (Jenkins 1991). GI symptoms were not reported in the tea drinkers. The absence of symptoms might be related to the hardness of the water, which is high in some areas of the United Kingdom. Jenkins (1991) reported finding unexpectedly high concentrations of fluoride (as high as 14 mg/L) in soft water compared with hard water when boiled. In contrast, in India, where endemic fluorosis is well documented, severe GI symptoms are common (Gupta et al. 1992; Susheela et al. 1993; Dasarathy et al. 1996). One cannot rule out the
### TABLE 9-1  Studies of Gastrointestinal Effects in Humans

<table>
<thead>
<tr>
<th>Approximate Concentration of Fluoride in the Stomach</th>
<th>Study Design</th>
<th>Findings</th>
<th>Application/Proposed Mechanisms</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water Fluoridation</strong></td>
<td></td>
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</tr>
<tr>
<td>1.0 mg/L</td>
<td>Case reports of patients (n = 52) drinking artificially fluoridated water.</td>
<td>Stomach cramps, abdominal pain, and nausea resolved when patients stopped drinking fluoridated water.</td>
<td>Possible gastrointestinal hypersensitivity.</td>
<td>Low daily dose of fluoride; cluster of subjects selected on the basis of symptoms.</td>
<td>Waldbott 1956</td>
</tr>
<tr>
<td>1.0 mg/L</td>
<td>Double-blinded test of patients (n = 60) drinking artificially fluoridated water in Haarlem, Netherlands.</td>
<td>50% of subjects had stomach and intestinal symptoms; 30% had stomatitis.</td>
<td>Possible gastrointestinal hypersensitivity.</td>
<td>Low daily dose of fluoride; self-reporting of symptoms.</td>
<td>Grimbergen 1974</td>
</tr>
<tr>
<td>1.0 mg/L</td>
<td>Case reports of symptoms in subjects (n = 20) drinking fluoridated water in Milwaukee.</td>
<td>Fatigue, pruritis, polydipsia, headaches, and gastrointestinal symptoms.</td>
<td>Possible gastrointestinal hypersensitivity.</td>
<td>Low daily dose; cluster of subjects selected on the basis of symptoms.</td>
<td>Petrabor 1977</td>
</tr>
<tr>
<td><strong>Water Fluoridation Accidents</strong></td>
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<tr>
<td>75-300 mg/L&lt;sup&gt;b&lt;/sup&gt; (range due to differences found in 2 fluoride feeders)</td>
<td>Symptoms reported in 34 children during accidental overfeed in school water supply.</td>
<td>Fluoride concentrations in water were 93.5 and 375 mg/L. 68% of the children had gastrointestinal upset.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Symptoms resolved after problem was corrected; doses of fluoride in mg/kg were not reported.</td>
<td>Hoffman et al. 1980</td>
</tr>
<tr>
<td>250 mg/L, (based on 50-mL ingestion)</td>
<td>Symptoms reported in 22 subjects during accidental overfeed in school water supply.</td>
<td>Fluoride concentration in water was 1,041 mg/L. 91% of the subjects had nausea and vomiting.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Only small amounts of the beverages made with the school's water were consumed.</td>
<td>Vogt et al. 1982</td>
</tr>
<tr>
<td>Concentration of Fluoride in the Stomach</td>
<td>Study Design</td>
<td>Findings</td>
<td>Comments</td>
<td>Reference</td>
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<tr>
<td>41 mg/L</td>
<td>Symptoms reported in 321 subjects during accidental overfeed in water supply.</td>
<td>Of the 160 persons who drank water; 52% had gastroenteritis. Only 2% of subjects who did not drink water reported gastroenteritis. Itching and skin rash also reported. Fluoride concentration in water was 150 mg/L.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Petersen et al. 1988</td>
<td></td>
</tr>
<tr>
<td>150 mg/L (assuming no dilution with stomach fluid)</td>
<td>Symptoms reported in 47 residents of a town during accidental fluoride overfeed of the water supply.</td>
<td>90% had nausea, vomiting, diarrhea, abdominal pains, or numbness or tingling of the face or extremities. One person in the town died. Fluoride concentration in water peaked at 51 mg/L.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Gessner et al. 1994</td>
<td></td>
</tr>
<tr>
<td>20-30 mg/L (based on 100-mL ingestion)</td>
<td>Symptoms reported in 39 patrons of a restaurant who consumed water or ice during an overfeed accident.</td>
<td>34 subjects had acute gastrointestinal illness in a 24-hour period after exposure. Fluoride concentration in water was 40 mg/L.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Penman et al. 1997</td>
<td></td>
</tr>
<tr>
<td>46-69 mg/L</td>
<td>Symptoms reported in 7 school children during accidental overfeed.</td>
<td>Nausea and vomiting. Fluoride concentration in water was 92 mg/L.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Sidhu and Kimmer 2002</td>
<td></td>
</tr>
</tbody>
</table>

*TABLE 9-1: Studies of Gastrointestinal Effects in Humans*
**TABLE 9-1 Continued**

<table>
<thead>
<tr>
<th>Approximate Concentration of Fluoride in the Stomach&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td><strong>Other Exposures</strong></td>
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<tr>
<td>5 ppm</td>
<td>Symptoms reported in pregnant women and their children from birth to 9 years taking NaF (1.2 mg) supplements. 672 cases (461 controls)</td>
<td>1% of cases had dermatologic, gastrointestinal, and neurologic effects. Comparisons with controls treated with binder placebo tablets established the effects to be from fluoride and not the binder.</td>
<td>Chronic or acute toxicity.</td>
<td>Details of clinical trial (e.g., randomization, stratification) not reported; dose in mg/kg was not reported; gastrointestinal systems were probably worse in small children (due to higher dose per kilogram of body weight).</td>
<td>Feltman and Kosel 1961</td>
</tr>
<tr>
<td>20 ppm, (assuming 100 of mL stomach fluid)</td>
<td>Symptoms observed in 10 adult volunteers who ingested 3 g of gel containing fluoride at 0.42% (4,200 mg/L).</td>
<td>Petechiae and erosion found in 7 of 10 subjects. Surface epithelium was most affected portion of the mucosa.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td>Approximately 10% of a probably toxic dose.</td>
<td>Spak et al. 1990</td>
</tr>
<tr>
<td>136 ppm (calculated from on 30 mg of NaF ingested in 100 mL of stomach fluid)</td>
<td>Symptoms observed in 10 patients with otosclerosis treated with NaF at 30 mg/day for 3-12 months.</td>
<td>7 subjects had abdominal pains, vomiting, and nausea. Endoscopy revealed petechiae, erosion, and erythema. Histological exams showed chronic atrophic gastritis in all patients and in only one of the controls.</td>
<td>Acute fluoride toxicity of the gastric epithelium.</td>
<td></td>
<td>Das et al. 1994</td>
</tr>
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<tr>
<td>200 ppm (using the 0.05% NaF mouthwash example)</td>
<td>Evaluation of reports to the American Association of Poison Control Centers of suspected overingestion of fluoride to estimate toxic amounts of home-use fluoride products.</td>
<td>Authors estimate a “probably toxic dose” of fluoride to children less than 6 years of age to be 50 mg. That dose was based on examples of a 10-kg child ingesting 10.1 g of 1.1% NaF gel; 32.7 g of 0.63% SnF₂ gel; 33.3 g of toothpaste with 1,500 ppm of fluoride; 50 g of toothpaste with 1,000 ppm of fluoride; or 221 mL of 0.05% NaF rinse.</td>
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<td>Chronic or acute toxicity. Details of clinical trial (e.g., randomization, stratification) not reported; dose in mg/kg was not reported; gastrointestinal systems were probably worse in small children (due to higher dose per kilogram of body weight).</td>
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aIn most studies, the concentration of fluoride in the stomach was not determined, so estimates were made by the committee. The actual concentrations could vary widely depending on the volume in the stomach and the rate of gastric secretions. The latter could also vary depending on the effect of fluoride (or any other agent) on the secretory process.

bEstimated from ingesting 400 mL of fluoridated water (unless dose was reported) diluted 0.8 with 100 mL of stomach fluid with fluoride at 1 mg/L (empty stomach).
influence of poor nutrition (the absence of dietary calcium in the stomach) contributing to the GI upset from fluoride ingestion. Chronic ingestion of drinking water rich in fluoride on an empty stomach is more likely to elicit symptoms.

**GI Symptoms Relating to the Concentration of Fluoride Intake**

It is important to realize that GI effects depend more on the net concentration of the aqueous solution of fluoride in the stomach than on the total fluoride dose in the fluid or solid ingested. The presence of gastric fluids already in the stomach when the fluoride is ingested can affect the concentration of the fluoride to which the gut epithelium is exposed. The residual volume of stomach fluid ranges between 15 and 30 mL in people fasting overnight (Narchi et al. 1993; Naguib et al. 2001; Chang et al. 2004). Such volumes would decrease the fluoride concentration of a glass of drinking water by only about 10%. In Table 9-1, the concentrations of fluoride in the stomach were estimated from the mean reported fluoride exposures. A dilution factor was used when it was clear that the subjects already had fluid in their stomach. The results from the water fluoridation overfeed reports (concentrations of fluoride in the stomach between 20 and 250 mg/L) indicate that GI symptoms, such as nausea and vomiting, are common side effects from exposure to high concentrations of fluoride.

Fluoride supplements are still routinely used today in areas where natural fluoride in the drinking water falls below 0.7 mg/L. In an early clinical trial using fluoride supplements, Feltman and Kosel (1961) administered fluoride tablets containing 1.2 mg of fluoride or placebo tablets to pregnant mothers and children up to 9 years of age. They determined that about 1% of the subjects complained of GI symptoms from the fluoride ingredient in the test tablets. If it is assumed that the stomach fluid volume after taking the fluoride supplement was approximately 250 mL, the concentration to which the stomach mucosal lining was exposed was in the neighborhood of 5 mg/L. GI effects appear to have been rarely evaluated in the fluoride supplement studies that followed the early ones in the 1950s and 1960s. Table 9-1 suggests that, as the fluoride concentration increases in drinking water, the percentage of the population with GI symptoms also increases. The table suggests that fluoride at 4 mg/L in the drinking water results in approximately 1% of the population experiencing GI symptoms (see Feltman and Kosel 1961).

**Chronic Moderate Dose Ingestion of Fluoride**

It is clear from the fluoride and osteoporosis clinical trial literature (also see Chapter 5) that gastric side effects were common in these studies (e.g.,
Mamelle et al. 1988; Hodsman and Drost 1989; Kleerekoper and Mendlovic 1993). Slow-release fluorides and calcium supplementation helped to reduce GI side effects (Kleerekoper and Mendlovic 1993; Das et al. 1994; Haguenauer et al. 2000). In areas of endemic fluorosis, such as parts of India, most subjects suffer from GI damage and adverse GI symptoms (Gupta et al. 1992; Susheela et al. 1993; Dasarathy et al. 1996). In one study (Susheela et al. 1993), every fourth person exposed to fluoride in drinking water (<1 to 8 mg/L) reported adverse GI symptoms. The results from these studies cannot be compared with the water fluoridation studies summarized in Table 9-1, because in the osteoporosis trials fluoride was nearly always administered as enteric coated tablets along with calcium supplements and the nutrition status of populations in endemic fluorosis areas is different from that in the United States.

Fluoride Injury Mechanisms in the GI Tract

Because 1% of the population is likely to experience GI symptoms, and GI symptoms are common in areas of endemic fluorosis, especially where there is poor nutrition (Gupta et al. 1992; Susheela et al. 1993; Dasarathy et al. 1996), it is important to understand the biological and physiological pathways for the effects of fluoride on the GI system. Those mechanisms have been investigated in many animal studies. In those studies, the concentrations of fluoride used were generally 100- to 1,000-fold higher than what occurs in the serum of subjects drinking fluoridated water. Although some tissues encounter enormous elevations in fluoride concentrations relative to the serum (e.g., kidney, bone), it is unlikely that the gut epithelium would be exposed to millimolar concentrations of fluoride unless there has been ingestion of large doses of fluoride from acute fluoride poisoning. During the ingestion of a large acute dose of fluoride such as fluoride-rich oral care products, contaminated drinking water during fluoridation accidents, and fluoride drugs for the treatment of osteoporosis, the consumption of large amounts of drinking water containing fluoride at 4 mg/L would serve only to aggravate the GI symptoms. Animal studies (see Table 9-2) have provided some important information on the mechanisms involved in GI toxicity from fluoride. Fluoride can stimulate secretion of acid in the stomach (Assem and Wan 1982; Shayiq et al. 1984), reduce blood flow away from the stomach lining, dilate blood vessels, increase redness of the stomach lining (Fujii and Tamura 1989; Whitford et al. 1997), and cause cell death and desquamation of the GI tract epithelium (Easmann et al. 1984; Pashley et al. 1984; Susheela and Das 1988; Kertesz et al. 1989; NTP 1990; Shashi 2002).

Because fluoride is a known inhibitor of several metabolic intracellular enzymes, it is not surprising that, at very high exposures, there is cell
<table>
<thead>
<tr>
<th>Species</th>
<th>Study Details</th>
<th>Findings</th>
<th>Possible Mechanisms/Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Circular muscle strips from the colons of colitic rats were treated with 10 mM NaF. Colitis was experimentally induced by intracolonic instillation of acetic acid.</td>
<td>NaF-induced contractions were significantly reduced in tissues from colitic rats compared with controls on days 2 and 3 postenema but not 14 days after enema. Results suggest that colitis alters smooth muscle contractility by disturbing elements in the signal transduction pathway distal to receptor activation of the G proteins.</td>
<td>Purpose of the study was to investigate whether colitis-induced decreases in the contraction of colonic smooth muscle is due to alteration in the excitation-contraction-coupling process at a site distal to receptor occupancy. Decrease in contractility might be due to impaired utilization of intracellular calcium.</td>
<td>Myers et al. 1997</td>
</tr>
<tr>
<td>Mouse</td>
<td>Isolated distended stomachs were treated with NaF at various concentrations (1-10 mM NaF).</td>
<td>Dose-related stimulation of H+ ion secretion. Stimulation of H+ ion secretion might be due to histamine release and increased formation of cyclic AMP (cAMP) in the gastric mucosa.</td>
<td>Fluoride might contribute to excess acid production in gastrointestinal tract.</td>
<td>Assem and Wan 1982</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>Isolated gastric chief cells treated with NaF (0-30 mM).</td>
<td>NaF increased intracellular diacylglycerol and Ca2+; 0.1 mM AlCl3 increased the effect of NaF.</td>
<td>Possible activation of a pertussis-toxin insensitive G protein coupled to a signal transducing mechanism. Action appears to be distinct from that activated by cholecystokinin.</td>
<td>Nakano et al. 1990</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Electronic chloride secretion by the jejunum was assessed by measuring short-circuit current variations (ΔIsc) due to alterations in ionic transport.</td>
<td>NaF induced a transient increase in Isc at &gt;5 mM; inhibited the antisecretory effect of peptide PYY and its analog P915 at 2 mM and decreased the stimulation of secretion by forskolin and dibutyryl cAMP by 50% at 2 mM. At 5 mM, inhibition of protein kinase C by bisindolylmaleimide caused a sustained increase in Isc.</td>
<td>NaF might reduce PYY-induced inhibition via a G-protein-dependent and a G-protein-independent functional pathway.</td>
<td>Eto et al. 1996</td>
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</table>
### TABLE 9-2
**Animal Studies of Gastrointestinal Effects and Mechanisms of Fluoride**

<table>
<thead>
<tr>
<th>Species</th>
<th>Study Findings</th>
<th>Possible Mechanisms/Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro Studies</strong></td>
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<td></td>
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<tr>
<td>Rat</td>
<td>Fluoride transport in intestinal brush border membrane vesicles examined.</td>
<td>Fluoride uptake by brush border membrane vesicles occurred rapidly and with an overshoot only in the presence of an inward-directed proton gradient. Fluoride transport occurs via a carrier-mediated process that might involve cotransport of fluoride with H⁺ or exchange of fluoride with OH⁻.</td>
<td>He et al. 1998</td>
</tr>
<tr>
<td>Mouse</td>
<td>Isolated distended stomachs were treated with NaF at various concentrations (1-10 mM NaF).</td>
<td>Dose-related stimulation of H⁺ ion secretion. Stimulation of H⁺ ion secretion might be due to histamine release and increased formation of cyclic AMP (cAMP) in the gastric mucosa. Fluoride might contribute to excess acid production in gastrointestinal tract.</td>
<td>Assem and Wan 1982</td>
</tr>
<tr>
<td>Guinea pig</td>
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<td>NaF increased intracellular diacylglycerol and Ca²⁺; 0.1 mM AlCl₃ increased the effect of NaF. Possible activation of a pertussis-toxin insensitive G protein coupled to a signal transducing mechanism. Action appears to be distinct from that activated by cholecystokinin.</td>
<td>Nakano et al. 1990</td>
</tr>
<tr>
<td>Rabbit</td>
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<td>He et al. 1998</td>
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</table>

**In Vivo Studies**

<table>
<thead>
<tr>
<th>Species</th>
<th>Study Findings</th>
<th>Possible Mechanisms/Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>25 mg/kg in drinking water for 60 days.</td>
<td>Increased gastric acidity and output. Elevation of cAMP concentrations in the gastric mucosa can stimulate H⁺ output, which might account for gastric symptoms reported in endemic fluorosis areas or from occupational exposure by inhalation.</td>
<td>Shayiq et al. 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>1 or 10 mM NaF (in 0.1 M HCl) placed in rat stomach for 1 hour.</td>
<td>Concentration- and time-dependent histological damage to the surface mucous cells. The higher concentration of NaF increased gastric permeability to small but not large molecules.</td>
<td>Pashley et al. 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>1, 10, or 50 mM NaF (in 0.1 M HCl) placed in rat stomach.</td>
<td>At 10 mM, desquamation of the surface mucous epithelial cells. At 50 mM, substantial damage to cells around the gastric gland openings and interfoveolar cell loss. Possible toxicity of the gut epithelium.</td>
<td>Easmann et al. 1984</td>
</tr>
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**continued**
<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
<th>Possible Mechanisms/Comments</th>
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<tbody>
<tr>
<td>Rat</td>
<td>100 mM NaF and 50 mM CaF&lt;sub&gt;2&lt;/sub&gt; intragastrically.</td>
<td>NaF-treated rats had extensive desquamation and cell injury. CaF&lt;sub&gt;2&lt;/sub&gt;-treated animals showed some desquamation and decrease in secretory activity.</td>
<td>Injury to stomach lining might affect secretion.</td>
<td>Kertesz et al. 1989</td>
</tr>
<tr>
<td>Rat</td>
<td>Single oral dose of NaF at 300 mg/kg.</td>
<td>Reduced blood flow from the stomach, reduced blood calcium, dilated blood vessels in the stomach, and redness.</td>
<td>Redness in the pyloric region of the stomach and intestine is likely due to a relaxation of the small veins, resulting in an accumulation of circulating blood in the mucosa of the intestinal tract.</td>
<td>Fujii and Tamura 1989</td>
</tr>
<tr>
<td>Rat</td>
<td>300 mg/L in drinking water for 6 months.</td>
<td>Gross lesions of the stomach in male rats. Diffuse mucosal hyperplasia with cellular necrosis in female rats.</td>
<td>Chronic fluoride toxicity of the gut epithelium.</td>
<td>NTP 1990</td>
</tr>
<tr>
<td>Rat</td>
<td>Stomachs of rats were instilled with 5 and 20 mM NaF for 1 hour.</td>
<td>Increased output of fluid, fucose, and galactose; marked reduction of titratable acidity of the lumen was pH dependent; and reduced amount of Alcian blue was bound to adherent mucus in a pH-independent manner.</td>
<td>Authors suggest that NaF accumulates with acid and acts as a barrier-breaking agent, rather than as a mucus-secretion stimulating agent.</td>
<td>Gharzouli et al. 2000</td>
</tr>
<tr>
<td>Mouse</td>
<td>NaF at 100 mg/L in drinking water for 30 days.</td>
<td>Organosomatic index decreased. Histopathologic changes of the intestine included increased number of goblet cells in the villi and crypts, cytoplasmic degranulation and vacuolation, nuclear pyknosis, abnormal mitosis, and lymphatic infiltration of submucosa and lamina propria.</td>
<td></td>
<td>Sondhi et al. 1995</td>
</tr>
<tr>
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<td>Study Details</td>
<td>Findings</td>
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<td>Mouse</td>
<td>NaF at 100 mg/L in drinking water for 30 days.</td>
<td>Organosomatic index decreased. Histopathologic changes of the intestine included increased number of goblet cells in the mucosal lining, cell death, and vacuolation, nuclear pyknosis, abnormal mitosis, and lymphatic infiltration of submucosa and lamina propria.</td>
<td>Sondhi et al. 1995</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>10 mg/kg/day by gavage for 2 years.</td>
<td>Morphologic abnormalities observed in all treated animals. “Cracked-clay” appearance of the microvilli surface of the duodenal epithelium and epithelial cell degeneration.</td>
<td>Susheela and Das 1988</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>Rabbits were given subcutaneous injections of 5, 10, 20, and 20 mg/kg/day for 15 weeks, and the duodenum was examined by histology.</td>
<td>Erosion and cell death of the surface mucosa, hemorrhage, cell death of Brunner’s gland, clumped submucosa, and hypertrophy of muscles in muscularis mucosae. Loss of mucosal layer was in direct proportion to NaF exposure. Injury to the intestine caused by cell death in the mucosal lining.</td>
<td>Shashi 2002</td>
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</tr>
<tr>
<td>Dog</td>
<td>Stomach mucosa with vascular supply intact was exposed to 1, 5, 10, 50, and 100 mM fluoride in different experiments.</td>
<td>At 5 and 10 mM fluoride, marked increases in the fluxes of water and sodium potassium, and hydrogen ions, mucus secretion, and tissue swelling and redness observed. Histopathologic exams showed marked thinning of the surface cell layer, reduced uptake of periodic acid Schiff stain, localized exfoliation and necrosis of surface cells, acute gastritis, and edema. Authors concluded that the threshold for effects on the structure and function of the gastric mucosa was approximately 1 mM fluoride.</td>
<td>Whitford et al. 1997</td>
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</table>

Whitford et al. 1997

http://www.nap.edu/catalog/11571.html
death and desquamation of the GI gut epithelium wall. The mechanisms involved in altering secretion remain unknown but are likely the result of fluoride’s ability to activate guanine nucleotide regulatory proteins (G proteins) (Nakano et al. 1990; Eto et al. 1996; Myers et al. 1997). Whether fluoride activates G proteins in the gut epithelium at very low doses (e.g., from fluoridated water at 4.0 mg/L) and has significant effects on the gut cell chemistry must be examined in biochemical studies.

THE RENAL SYSTEM

The kidney is the organ responsible for excreting most of the fluoride. It is exposed to concentrations of fluoride about five times higher than in other organs, as the tissue/plasma ratio for the kidney is approximately 5 to 1, at least in the rat (Whitford 1996). Kidneys in humans may be exposed to lower fluoride concentrations than in rats. Human kidneys, nevertheless, have to concentrate fluoride as much as 50-fold from plasma to urine. Portions of the renal system may therefore be at higher risk of fluoride toxicity than most soft tissues. In this section, three aspects of kidney function are discussed in the context of fluoride toxicity. First, can long-term ingestion of fluoride in drinking water at 4 mg/L contribute to the formation of kidney stones? Second, what are the mechanisms of fluoride toxicity on renal tissues and function? And third, what special considerations have to be made in terms of residents who already have kidney failure and who are living in communities with fluoride at 4 mg/L in their drinking water?

Does Fluoride in Drinking Water Contribute to Kidney Stones?

Early water fluoridation studies did not carefully assess changes in renal function. It has long been suspected that fluoride, even at concentrations below 1.2 mg/L in drinking water, over the years can increase the risk for renal calculi (kidney stones). Research on this topic, on humans and animals, has been sparse, and the direction of the influence of fluoride (promotion or prevention of kidney stones) has been mixed (Table 9-3; Juuti and Hei nonen 1980; Teotia et al. 1991; Li et al. 1992; Shashi et al. 2002). Singh et al. (2001) carried out an extensive examination of more than 18,700 people living in India where fluoride concentrations in the drinking water ranged from 3.5 to 4.9 mg/L. Patients were interviewed for a history of urolithiasis (kidney stone formation) and examined for symptoms of skeletal fluorosis, and various urine and blood tests were conducted. The patients with clear signs and symptoms of skeletal fluorosis were 4.6 times more likely to develop kidney stones. Because the subjects of this study were likely at greater risk of kidney stone formation because of malnutrition, similar research should be conducted in North America in areas with fluoride at 4 mg/L.
in the drinking water. It is possible that the high incidence of uroliths is related to the high incidence of skeletal fluorosis, a disorder that has not been studied extensively in North America. If fluoride in drinking water is a risk factor for kidney stones, future studies should be directed toward determining whether kidney stone formation is the most sensitive end point on which to base the MCLG.

Mechanisms of Fluoride Toxicity on Kidney Tissue and Function

Fluoride in acute and chronic doses can dramatically affect the kidney, but, again, it is the dose that is important. People living in fluoridated areas (at 1.0 mg/L) drinking 1.0 L of water a day will consume 1 mg of fluoride a day (less than 0.014 mg/kg for the average 70-kg person). There are no published studies that show that fluoride ingestion on a chronic basis at that concentration can affect the kidney. However, people living in an area where the drinking water contains fluoride at 4 mg/L who consume 2-3 L of water per day will ingest as much as 12 mg fluoride per day on a chronic basis (see Chapter 2). On the basis of studies carried out on people living in regions where there is endemic fluorosis, ingestion of fluoride at 12 mg per day would increase the risk for some people to develop adverse renal effects (Singh et al. 2001).

Humans can be exposed to even higher acute doses of fluoride either unintentionally (water fluoridation accidents, hemodialysis accidents, accidental poisoning) or intentionally, such as from fluorinated general anesthetics. Administration of certain halothane anesthetics, which are defluorinated by the liver, can result in serum fluoride concentrations that are 50-fold higher than normal, and those concentrations are maintained during surgery and well afterward (see Table 9-3 and Chapter 2). These concentrations of fluoride in the serum have been associated with nephrotoxicity, but most of the symptoms resolve after surgery when fluoride concentrations are allowed to decline. Although it is unlikely that consuming fluoridated drinking water could lead to such high serum fluoride concentrations, one has to consider that subjects who already have impaired kidney function and are unable to excrete fluoride efficiently will retain more fluoride. At this time, there are no studies to distinguish between adverse effects produced by fluoride and the defluorinated metabolites of fluorinated general anesthetics. Therefore, it is plausible that the defluorinated metabolites are responsible for some, most, or even all of the side effects on the kidneys.

Animal studies have helped in determining just how the kidney responds to high doses of fluoride. Borke and Whitford (1999) showed that ATP-dependent calcium uptake in rat kidneys was significantly affected by exposures equivalent to that of patients undergoing hemodialysis. Cittanova et al. (2002) showed that high concentrations of fluoride affected the ATPase
TABLE 9-3 Renal Effects of Fluoride

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
<th>Proposed Mechanisms</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Renal Stone Formation</strong></td>
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<tr>
<td>Human</td>
<td>Incidence of renal stones in Finnish hospital districts with different concentrations of fluoride in drinking water, in a fluoridated community, and a nonfluoridated city.</td>
<td>At fluoride concentrations of 1.5 mg/L or greater, the standardized hospital admission rates for urolithiasis was increased about one-sixth. No differences were found with fluoride concentrations of ≤0.49 mg/L and 0.50-1.49 mg/L. A separate comparison of a fluoridated city (1 mg/L) and a referent city (&lt;0.49 mg/L) found a 25% lower rate of urolithiasis in the fluoridated city.</td>
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<tr>
<td>Human</td>
<td>20 children with vesical stones were evaluated for fluoride intake and content of renal stones.</td>
<td>Mean fluoride intake was 2.5 ± 0.8 mg in 24 hours. Subjects had normal plasma and urinary excretion of fluoride. No statistically significant difference in fluoride content between the center and periphery of the stones. Fluoride content was higher in stones with calcium than in those with uric acid or ammonium urate. Authors conclude that fluoride does not cause initiation or growth of the nucleus of vesical stones.</td>
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<tr>
<td>Human</td>
<td>18,706 tribal people from fluoride endemic and nonendemic areas of India were evaluated for history of renal stones.</td>
<td>In endemic areas, fluoride in drinking water was 3.5-4.9 mg/L. Prevalence of urolithiasis was 4.6 times higher in the endemic area than in the nonendemic area. In the endemic area, subjects with fluorosis had nearly double the prevalence of urolithiasis compared with those without fluorosis.</td>
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<tr>
<td>Rat</td>
<td>Effect of NaF on ethylene glycol-induced renal stone formation in rats.</td>
<td>NaF reduced oxalate stone production.</td>
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<tr>
<td><strong>Toxic Effects of Fluoride on Kidney Tissues and Function</strong></td>
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</tr>
<tr>
<td>Human</td>
<td>Renal function evaluated in 30 patients exposed by inhalation to sevoflurane compared with 25 controls exposed to isoflurane.</td>
<td>Mean peak plasma fluoride was 29.3 ± 1.8 µmol/L 2 hours after anesthesia and 18 µmol/L after 8 hours. Five patients had peak concentrations of greater than 50 µmol/L. No lasting renal or hepatic functional changes found.</td>
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<tr>
<td>Species Study Findings</td>
<td>Comments</td>
<td>Reference</td>
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<td>At fluoride concentrations of 1.5 mg/L or greater, the standardized hospital admission rates for urolithiasis was increased about one-sixth. No differences were found with fluoride concentrations of $\leq 0.49$ mg/L and 0.50-1.49 mg/L. A separate comparison of a fluoridated city (1 mg/L) and a referent city (&lt;0.49 mg/L) found a 25% lower rate of urolithiasis in the fluoridated city.</td>
<td>Juuti and Heinonen 1980</td>
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<tr>
<td>Human 20 children with vesical stones were evaluated for fluoride intake and content of renal stones. Mean fluoride intake was 2.5 ± 0.8 mg in 24 hours. Subjects had normal plasma and urinary excretion of fluoride. No statistically significant difference in fluoride content between the center and periphery of the stones. Fluoride content was higher in stones with calcium than in those with uric acid or ammonium urate. Authors conclude that fluoride does not cause initiation or growth of the nucleus of vesical stones. Fluoride’s role as a promoter of kidney stones was ruled out but this is based on a small sample size. The authors did not study nephrolithiasis and excessive chronic fluoride intake.</td>
<td></td>
<td>Teotia et al. 1991</td>
<td></td>
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<tr>
<td>Human 18,706 tribal people from fluoride endemic and nonendemic areas of India were evaluated for history of renal stones. In endemic areas, fluoride in drinking water was 3.5-4.9 mg/L. Prevalence of urolithiasis was 4.6 times higher in the endemic area than in the nonendemic area. In the endemic area, subjects with fluorosis had nearly double the prevalence of urolithiasis compared with those without fluorosis. Lack of nutrition in the population leads to increases in oxalate excretion. Oxalate increases oxidative load, which increases cellular damage where urinary crystals have an opportunity to grow. Fluoride contributes to the oxidative load and passively participates in renal crystal formation. Water fluoride concentration was at EPA’s current MCLG, but malnutrition among the study population probably made risk for renal stones higher.</td>
<td></td>
<td>Singh et al. 2001</td>
<td></td>
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</tr>
<tr>
<td>Rat Effect of NaF on ethylene glycol-induced renal stone formation in rats. NaF reduced oxalate stone production. NaF inhibition of induced renal stones appears to be due to its ability to decrease oxalate synthesis and urinary oxalate excretion. Decreased urinary oxalate secretion might be a toxic effect on the kidneys.</td>
<td></td>
<td>Li et al. 1992</td>
<td></td>
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</tr>
<tr>
<td>Toxic Effects of Fluoride on Kidney Tissues and Function</td>
<td>Renal function evaluated in 50 patients exposed by inhalation to sevoflurane compared with 25 controls exposed to isoflurane. Mean peak plasma fluoride was 29.3 ± 1.8 µmol/L 2 hours after anesthesia and 18 µmol/L after 8 hours. Five patients had peak concentrations of greater than 50 µmol/L. No lasting renal or hepatic functional changes found.</td>
<td>Frink et al. 1992</td>
<td></td>
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</table>

*continued*
### Human

#### Renal damage evaluated in 23 patients exposed by inhalation to sevoflurane compared with 11 controls exposed to isoflurane.

- 8 patients had serum fluoride concentrations > 50 µmol/L. An inverse correlation was found between peak fluoride concentration and maximal urinary osmolality after the injection of vasopressin ($r = -0.42, P < 0.05$). Increased urinary N-acetyl-β-glucosaminidase excretion, but no lasting damage to the kidney.

#### Immortalized ascending duct cells of kidneys were incubated with 0-100 mM fluoride.

- Fluoride decreased cell number by 23% ($P < 0.05$), total protein content by 30% ($P < 0.05$), and hydrogen-leucine incorporation by 43% ($P < 0.05$). LDH release was increased by 236% ($P < 0.05$), with a threshold of 5 mM. There was also a 58% reduction in Na,K-ATPase activity at 5 mM ($P < 0.05$). Crystal formations found in mitochondria.

#### Renal function evaluated in 50 patients exposed by inhalation to sevoflurane.

- Mean peak plasma fluoride was $28.2 \pm 14$ µmol/L 1 hour after exposure. 2 patients had concentrations > 50 µmol/L 12-24 hours after anesthesia and raised blood urea nitrogen and creatinine concentrations.

#### Health survey of residents of rural areas in China exposed to airborne fluoride from combustion of coal.

- Glomerular filtration rate was affected, as shown by significantly lower urinary inorganic phosphate concentrations in exposed populations compared with control populations.

#### Effects of fluoride on renal acid phosphatases in the afferent arterioles and in glomeruli.

- Alkaline fixation-resistant and lysosomal acid phosphatase activities were significantly inhibited at 75 µM. Tartrate-resistant activity was also significantly inhibited at 250 µM.

#### Renal function in Chinese children (n = 210) exposed to different concentrations of fluoride in drinking water. Subjects stratified into 7 groups (n = 30), including controls. Comparisons made between subjects with “high fluoride load” and enamel fluorosis (details not provided) in areas with fluoride at <1.0, 1.0-2.0, 2.0-3.0, and >3.0 mg/L.

- Significant increase in urine NAG and gamma-GT activities in children with enamel fluorosis exposed to fluoride at 2.58 mg/L and in children exposed at 4.51 mg/L. Dose-response relationship observed between fluoride concentration and these two measures of renal damage.
<table>
<thead>
<tr>
<th>Proposed Mechanisms</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrion appears to be the target of fluoride toxicity in collecting duct cells. Effects are partly responsible for the urinary concentrating defects in patients after administration of biotransformed inhaled anesthetics.</td>
<td>Authors concluded that sevoflurane might induce nephrotoxicity.</td>
<td>Cittanova et al. 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Goldberg et al. 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ando et al. 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partanen 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects were similar with respect to age, gender, and nutritional status.</td>
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</tbody>
</table>

*TABLE 9-3 Continued*

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Fluoride in Drinking Water: A Scientific Review of EPA’s Standards
http://www.nap.edu/catalog/11571.html
**TABLE 9-3 Continued**

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>NaF 10, 50, 150 mg/L in drinking water for 6 weeks.</td>
<td>Plasma fluoride concentrations were &lt;0.4, 2, 7, and 35 µmol/L, respectively. ATP-dependent 45Ca uptake was significantly lower in the high exposure group than in controls ($P &lt; 0.05$). Thapsigargin treatment showed that the lower uptake was associated with significantly lower activities of both the plasma membrane Ca$^{2+}$-pump (in high-dose group compared with controls, $P &lt; 0.05$) and endoplasmic reticulum Ca$^{2+}$-pump (in the mid- and high-dose groups compared with controls, $P &lt; 0.05$). <strong>Ca$^{2+}$ homeostasis appears to have been affected by an increase in turnover or breakdown or decreasing the expression of plasma membrane and endoplasmic reticulum Ca$^{2+}$-pump proteins.</strong></td>
</tr>
<tr>
<td>Rat</td>
<td>30 and 100 mg/L in drinking water for 7 months.</td>
<td>Decreased phosphatidylethanolamine and phosphatidylcholine phospholipids and ubiquinon in the kidney. Increased lipid peroxidation. Electron microscopy revealed alterations in renal structures, including mitochondrial swelling in the proximal convoluted tubules and decreased numbers of microvilli and disintegrated brush border at the luminal surface. <strong>The pathogenesis of chronic fluorosis might be due to oxidative stress and modification of cellular membrane lipids. Those alterations might explain observed systemic effects, especially in soft tissues and organs.</strong></td>
</tr>
<tr>
<td>Rat (in vitro)</td>
<td>Kidney epithelial cells (NRK-52E) were cultured with NaF.</td>
<td>Calcium accumulation was significantly increased.</td>
</tr>
<tr>
<td>Rabbit (in vitro)</td>
<td>Immortalized kidney cells of the thick ascending limb were cultured with 1, 5, or 10 mmol of NaF for 24 hours; or 5 mmol for 1, 5, and 10 hours.</td>
<td>At 5 mmol after 24 hours, fluoride decreased cell numbers by 14% ($P &lt; 0.05$), protein content by 16%, leucine incorporation by 54%, and Na-K-2Cl activity by 84%. There was a 145% increase in LDH and a 190% increase in N-acetyl-β-glucosaminidase release. Na,K-ATPase activity was significantly impaired at 1 mmol for 24 hours and after 2 hours at 5 mmol. <strong>Na,K-ATPase pump appears to be a major target of fluoride toxicity in the loop of Henle.</strong></td>
</tr>
<tr>
<td>Rabbit</td>
<td>NaF at 5, 10, 20, and 50 mg/kg/day injected subcutaneously for 15 weeks.</td>
<td>At 10 mg/kg/day and higher, increased cloudy swellings, degeneration of the tubular epithelium, cell death, vacuolization of the renal tubules, hypertrophy and atrophy of the glomeruli, exudation, interstitial edema, and interstitial nephritis.</td>
</tr>
<tr>
<td>Proposed Mechanisms</td>
<td>Comments</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ca(^2+) homeostasis appears to have been affected by an increase in turnover or breakdown or decreasing the expression of plasma membrane and endoplasmic reticulum Ca(^2+)-pump proteins.</td>
<td></td>
<td>Borke and Whitford 1999</td>
</tr>
<tr>
<td>The pathogenesis of chronic fluorosis might be due to oxidative stress and modification of cellular membrane lipids. Those alterations might explain observed systemic effects, especially in soft tissues and organs.</td>
<td></td>
<td>Guan et al. 2000</td>
</tr>
<tr>
<td>Elevation of ER-type Ca(^2+)ATPase activity appears to operate as a regulatory system to protect against large increases in cytosolic calcium concentrations due to increased influx of calcium into the ER.</td>
<td></td>
<td>Murao et al. 2000</td>
</tr>
<tr>
<td>Na,K-ATPase pump appears to be a major target of fluoride toxicity in the loop of Henle.</td>
<td></td>
<td>Cittanova et al. 2002</td>
</tr>
<tr>
<td>Mechanism for the damage not proposed</td>
<td></td>
<td>Shashi et al. 2002</td>
</tr>
</tbody>
</table>

*continued*
**Fluoride Toxicity in Hemodialysis Patients**

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Plasma and bone concentrations of fluoride and renal osteodystrophy in HD patients</td>
<td>Mean plasma concentration of fluoride was 10.8 µmol/L in 34 patients with residual glomerular filtration rates (RGFR) and 15.6 µmol/L in 25 patients with anuria. Mean bone ash concentration of fluoride was 5,000 mg/kg in 14 patients with RGFR and 7,200 mg/kg in 26 patients with anuria. Evidence of secondary hyperparathyroidism. Evidence of osteodystrophy reported, but did not appear to be of the advanced degree found with skeletal fluorosis.</td>
</tr>
<tr>
<td>Human</td>
<td>Comparison of serum fluoride concentrations in 17 HD patients and 17 CAPD patients.</td>
<td>Higher serum fluoride concentrations found in HD patients (4.0 ± 0.5 µmol/L) compared with CAPD patients (2.5 ± 0.3 µmol/L), <em>P</em> &lt; 0.005.</td>
</tr>
<tr>
<td>Human</td>
<td>Renal osteodystrophy in 209 HD patients in Saudi Arabia.</td>
<td>Bone and joint pain reported in 25.8% of patients. The major radiological finding was osteosclerosis in 70% of patients. Mean serum concentration of aluminum was 25.4 ± 17.7 µg/L; of 1,25-dihydroxy vitamin D3 was 8.1 ± 4.2 ng/L; and of fluoride was 92.2 ± 31.4 µg/L.</td>
</tr>
<tr>
<td>Human</td>
<td>Effects on plasma potassium concentration of 25 HD patients from mineral water containing fluoride at 9 mg/L.</td>
<td>There was a significant correlation between plasma fluoride and potassium concentrations before dialysis (<em>P</em> &lt; 1 × 10⁻⁷) but not after. Group-by-group comparisons indicated that the correlation was linked to the group consuming the mineral water (<em>P</em> &lt; 1 × 10⁻⁷), which had higher plasma potassium concentrations before dialysis than the group that did not drink the mineral water (<em>P</em> &lt; 0.005).</td>
</tr>
<tr>
<td>Human</td>
<td>Serum fluoride concentrations evaluated in 29 HD patients.</td>
<td>Serum fluoride was significantly higher in patients before and after HD than in healthy subjects. Despite net clearance of fluoride during HD, serum fluoride did not return to normal concentrations.</td>
</tr>
</tbody>
</table>
### Proposed Mechanisms

<table>
<thead>
<tr>
<th>Species Study</th>
<th>Findings</th>
<th>Proposed Mechanisms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride Toxicity in Hemodialysis Patients</td>
<td>Human Plasma and bone concentrations of fluoride and renal osteodystrophy in HD patients</td>
<td>The bone concentrations of fluoride fall within the ranges historically associated with stage II and stage III skeletal fluorosis (see Chapter 5). The study reported no skeletal fluorosis, but it was unclear what criteria were used for assessment of the condition. Suggests bone concentrations alone do not adequately predict skeletal fluorosis.</td>
<td>Erben et al. 1984</td>
</tr>
<tr>
<td>Human Comparison of serum fluoride concentrations in 17 HD patients and 17 CAPD patients.</td>
<td>Higher serum fluoride concentrations found in HD patients (4.0 ± 0.5 µmol/L) compared with CAPD patients (2.5 ± 0.3 µmol/L), P &lt; 0.005.</td>
<td>Authors noted that fluoride content of the HD fluids, which were prepared with fluoridated water, was significantly higher than in commercially prepared peritoneal dialysis fluid.</td>
<td>Bello and Gitelman 1990</td>
</tr>
<tr>
<td>Human Renal osteodystrophy in 209 HD patients in Saudi Arabia.</td>
<td>Bone and joint pain reported in 25.8% of patients. The major radiological finding was osteosclerosis in 70% of patients. Mean serum concentration of aluminum was 25.4 ± 17.7 µg/L; of 1,25-dihydroxy vitamin D3 was 8.1 ± 4.2 ng/L; and of fluoride was 92.2 ± 31.4 µg/L.</td>
<td>Osteodystrophy could be related to aluminum exposure. Water quality in Saudi Arabia is not the same as in the United States.</td>
<td>Huraib et al. 1993</td>
</tr>
<tr>
<td>Human Effects on plasma potassium concentration of 25 HD patients from mineral water containing fluoride at 9 mg/L.</td>
<td>There was a significant correlation between plasma fluoride and potassium concentrations before dialysis (P &lt; 1 × 10–7) but not after. Group-by-group comparisons indicated that the correlation was linked to the group consuming the mineral water (P &lt; 1 × 10–7), which had higher plasma potassium concentrations before dialysis than the group that did not drink the mineral water (P &lt; 0.005).</td>
<td></td>
<td>Nicolay et al. 1999</td>
</tr>
<tr>
<td>Human Serum fluoride concentrations evaluated in 29 HD patients.</td>
<td>Serum fluoride was significantly higher in patients before and after HD than in healthy subjects. Despite net clearance of fluoride during HD, serum fluoride did not return to normal concentrations.</td>
<td></td>
<td>Usuda et al. 1997</td>
</tr>
</tbody>
</table>

*continued*
TABLE 9-3 Continued

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Serum fluoride concentrations evaluated in 39 patients with end stage renal disease living in an area with fluoride at 47.4 ± 3.28 µM/L in drinking water. 30 patients treated with HD and 9 with CAPD.</td>
<td>Mean serum fluoride was significantly higher in dialysis patients (2.67 ± 1.09 µM/L) than in controls. CAPD patients had higher mean fluoride concentrations (3.1 ± 1.97 µM/L) than HD patients (2.5 ± 1.137 µM/L). 39% of dialysis patients had serum fluoride concentrations &gt; 3.0 µM/L, a concentration believed to pose a risk of osteodystrophy.</td>
</tr>
<tr>
<td>Human</td>
<td>Plasma fluoride concentrations measured in 35 dialysis patients.</td>
<td>Highly significant correlation between fluoride concentrations before and after dialysis ($P &lt; 0.00001$) and between the months of hemodialysis and average fluoride concentration before dialysis ($r = 0.624; P = 0.008$).</td>
</tr>
<tr>
<td>Human</td>
<td>Serum fluoride concentrations measured in 150 dialysis patients.</td>
<td>Serum fluoride concentrations were approximately 3.3 times higher in dialysis patients than in healthy subjects.</td>
</tr>
<tr>
<td>Human</td>
<td>153 iliac crest bone biopsies from renal osteodystrophy patients were analyzed.</td>
<td>Increase in bone fluoride was weakly associated with increased osteoid volume, surface, and thickness. Bone fluoride had a negative correlation with bone microhardness.</td>
</tr>
</tbody>
</table>

**Hemodialysis Accidents**

| Human   | Evaluation of 12 patients who became severely ill after HD treatment and 20 patients who did not become ill after treatment in the same unit. | 12 of 15 patients treated in one room had severe pruritus, multiple nonspecific symptoms, and/or fatal ventricular fibrillation (3 patients). Serum fluoride concentration in ill patients was as high as 716 µmol/L. 20 patients treated in a different room did not become ill ($P < 0.0001$). |

**ABBREVIATIONS:** CAPD, continuous ambulatory peritoneal dialysis; ER, endoplasmic reticulum; GT, glutamyltransferase; HD, hemodialysis; LDH, lactate dehydrogenase; NAG, N-acetyl-beta-D-glucosaminidase.

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[Links to related pages]
<table>
<thead>
<tr>
<th>Proposed Mechanisms</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride incorporation at the mineralizing front increases mineralization lag time.</td>
<td>The authors speculated that accumulated fluoride interacted with aluminum in dialysis patients, altering bone properties.</td>
<td>Al-Wakeel et al. 1997</td>
</tr>
<tr>
<td></td>
<td>Water used for dialysis in the ill patients was found to have excessive concentrations of fluoride because of errors in maintenance of the deionization system.</td>
<td>Nicolay et al. 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Torra et al. 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ng et al. 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arnow et al. 1994</td>
</tr>
</tbody>
</table>

**TABLE 9-3**

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pump in cultured rabbit ascending loop cells. Guan et al. (2000) showed that the same concentrations of fluoride that caused dental fluorosis in rats affected kidney phospholipids. Rat studies show that the animals that had most of their renal tissue surgically removed retained more fluoride in their bones, which became more susceptible to fracture (Turner et al. 1996). Turner’s rat studies were also conducted to simulate the concentrations that humans would be exposed to in regions where the drinking water contained fluoride at 3-10 mg/L.

Patients with Renal Impairment

Several investigators have shown that patients with impaired renal function, or on hemodialysis, tend to accumulate fluoride much more quickly than normal. Patients with renal osteodystrophy can have higher fluoride concentrations in their serum (see Table 9-3). Whether some bone changes in renal osteodystrophy can be attributed to excess bone fluoride accumulation alone, or in combination with other elements such as magnesium and aluminum, has not been clearly established (Erben et al. 1984; Huraib et al. 1993; Ng et al. 2004). Extreme caution should be used in patients on hemodialysis because failures of the dialysis equipment have occurred in the past, resulting in fluoride intoxication (Arnow et al. 1994).

HEPATIC SYSTEM

Although some studies have observed histopathologic changes in the liver in response to high doses of fluoride (Kapoor et al. 1993; Grucka-Mameczar et al. 1997), the changes have not been carefully quantified. In a study to examine the histologic effects of NaF directly on the liver, rats fed 5-50 mg/kg/day showed vacuolization of the hepatic cells, cellular necrosis, and dilated and engorged liver tissue that was not seen in the control animals (Shashi and Thapar 2001).

In some of the studies in which effects of chronic or acute fluoride doses were observed in kidneys, the livers were also examined for signs of toxicity. Tormanen (2003) showed that fluoride caused substrate inhibition of rat liver arginase at substrate concentrations above 4 mM, and rat kidney arginase was more sensitive than liver arginase to inhibition by fluoride. de Camargo and Merzel (1980) first reported significant increases in fatty deposits in the livers of rats but not in their kidneys when they were given NaF at 1, 10, or 100 mg/L in tap water for 180 days. Twenty years later, Wang et al. (2000) used high-performance liquid chromatography to document the changes in liver lipids after rats were fed drinking water with fluoride at 30 or 100 mg/L for 7 months. The higher concentration of fluoride reduced total phospholipids. Within the phospholipids, the saturated
fatty acid components increased and polyunsaturated fatty acids decreased. Liver cholesterol and dolichol were unchanged. The authors concluded that fluoride-induced alteration in liver membrane lipids could be an important factor in the pathogenesis of chronic fluorosis.

Whether any of these changes has relevance to the long-term daily ingestion of drinking water containing fluoride at 4 mg/L will require careful analysis of liver function tests in areas with high and low concentrations of fluoride in the drinking water. The clinical trials involving fluoride therapy for treating osteoporosis require that subjects be administered fluoride at concentrations approaching 1.0 mg/kg/day. Although such studies are rarely carried out for more than 5 years, this period of time should be sufficient to measure any changes in hepatic function. Jackson et al. (1994) reported that there was a significant increase in liver function enzymes in test subjects taking 23 mg of fluoride a day for 18 months, but the enzyme concentrations were still within the normal range. It is possible that a lifetime ingestion of 5-10 mg/day from drinking water containing fluoride at 4 mg/L might turn out to have long-term effects on the liver, and this should be investigated in future epidemiologic studies.

Finally, because the liver is the primary organ for defluorinating toxic organofluorides, there is a concern that added fluoride body burden that would be experienced in areas where the drinking water had fluoride at 4 mg/L might interfere with the activity of the cytochrome P450 complex (Baker and Ronnenberg 1992; Kharasch and Hankins 1996).

IMMUNE SYSTEM

Hypersensitivity

In the studies by physicians treating patients who reported problems after fluoridation was initiated, there were several reports of skin irritation (Waldbott 1956; Grimbergen 1974; Petraborg 1977). Although blinded experiments suggested that the symptoms were the result of chemicals in the water supply, various anecdotal reports from patients complaining, for example, of oral ulcers, colitis, urticaria, skin rashes, nasal congestion, and epigastric distress, do not represent type I (anaphylactic), II (cytotoxic), III (toxic complex), or IV (delayed type reactivity) hypersensitivity, according to the American Academy of Allergy (Austen et al. 1971). These patients might be sensitive to the effects of silicofluorides and not the fluoride ion itself. In a recent study, Machalinski et al. (2003) reported that the four different human leukemic cell lines were more susceptible to the effects of sodium hexafluorosilicate, the compound most often used in fluoridation, than to NaF.

Nevertheless, patients who live in either an artificially fluoridated com-
munity or a community where the drinking water naturally contains fluoride at 4 mg/L have all accumulated fluoride in their skeletal systems and potentially have very high fluoride concentrations in their bones (see Chapter 3). The bone marrow is where immune cells develop and that could affect humoral immunity and the production of antibodies to foreign chemicals. For example, Butler et al. (1990) showed that fluoride can be an adjuvant, causing an increase in the production of antibodies to an antigen and an increase in the size and cellularity of the Peyer’s patches and mesenteric lymph nodes. The same group (Loftenius et al. 1999) then demonstrated that human lymphocytes were more responsive to the morbilli antigen. Jain and Susheela (1987), on the other hand, showed that rabbit lymphocytes exposed to NaF had reduced antibody production to transferrin.

At the very early stages of stem cell differentiation in bone, fluoride could affect which cell line is stimulated or inhibited. Kawase et al. (1996) suggested that NaF (0.5 mM for 0-4 days) stimulates the granulocytic pathway of the progenitor cells in vitro. This was confirmed by Oguro et al. (2003), who concluded that “NaF [<0.5 mM] induces early differentiation of bone marrow hemopoietic progenitor cells along the granulocytic pathway but not the monocytic pathway.”

It has long been claimed that cells do not experience the concentrations of fluoride that are used in vitro to demonstrate the changes seen in cell culture. Usually millimolar concentrations are required to observe an effect in culture. Because serum fluoride normally is found in the micromolar range, it has been claimed that there is no relevance to the in vivo situation. However, studies by Okuda et al. (1990) on resorbing osteoclasts reported that: “NaF in concentrations of 0.5-1.0 mM decreased the number of resorption lacunae made by individual osteoclasts and decreased the resorbed area per osteoclast. We argue that the concentration of fluoride in these experiments may be within the range ‘seen’ by osteoclasts in mammals treated for prolonged periods with approximately 1 mg of NaF/kg body weight (bw) per day.” Sodium fluoride intake at 1 mg/kg/day in humans could result in bone fluoride concentrations that might occur in an elderly person with impaired renal function drinking 2 L of water per day containing fluoride at 4 mg/L (see Chapters 3 and 5 for more information on bone fluoride concentrations).

Cellular Immunity

Macrophage function is a major first line of defense in immunity. When macrophage function is impaired, the body could fail to control the invasion of foreign cells or molecules and their destructive effects. The studies that have investigated the function of the cells involved in humoral immunity are summarized in Table 9-4.
Fluoride, usually in the millimolar range, has a number of effects on immune cells, including polymorphonuclear leukocytes, lymphocytes, and neutrophils. Fluoride interferes with adherence to substrate in vitro. The variety of biochemical effects on immune cells in culture are described in Table 9-4. Fluoride also augments the inflammatory response to irritants. Several mechanisms have been proposed, and the main route is thought to be by means of activation of the G-protein complex. It appears that aluminum combines with fluoride to form aluminum fluoride, a potent activator of G protein. In a study by O’Shea et al. (1987), for example, AlF$_4^{-}$ had a greater influence on lymphocyte lipid metabolism than did fluoride in the absence of aluminum. On the other hand, Goldman et al. (1995) showed that the aluminofluoride effect of activating various enzymes in macrophages is independent of the G-protein complex.

There is no question that fluoride can affect the cells involved in providing immune responses. The question is what proportion, if any, of the population consuming drinking water containing fluoride at 4.0 mg/L on a regular basis will have their immune systems compromised? Not a single epidemiologic study has investigated whether fluoride in the drinking water at 4 mg/L is associated with changes in immune function. Nor has any study examined whether a person with an immunodeficiency disease can tolerate fluoride ingestion from drinking water. Because most of the studies conducted to date have been carried out in vitro and with high fluoride concentrations, Challacombe (1996) did not believe they warranted attention. However, as mentioned previously in this chapter, bone concentrates fluoride and the blood-borne progenitors could be exposed to exceptionally high fluoride concentrations. Thus, more research needs to be carried out before one can state that drinking water containing fluoride at 4 mg/L has no effect on the immune system.

**FINDINGS**

The committee did not find any human studies on drinking water containing fluoride at 4 mg/L where GI, renal, hepatic, or immune effects were carefully documented. Most reports of GI effects involve exposures to high concentrations of fluoride from accidental overfeeds of fluoride into water supplies or from therapeutic uses. There are a few case reports of GI upset in subjects exposed to drinking water fluoridated at 1 mg/L. Those effects were observed in only a small number of cases, which suggest hypersensitivity. However, the available data are not robust enough to determine whether that is the case.

Studies of the effects of fluoride on the kidney, liver, and immune system indicate that exposure to concentrations much higher than 4 mg/L can affect renal tissues and function and cause hepatic and immunologic alterations.
TABLE 9-4 Effects of Fluoride on Immune System Cells

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Metabolism factors measured in cultured PMNs incubated with mM concentrations of fluoride.</td>
<td>Significant inhibition of PMN metabolic activity at 0.1 mM fluoride for O2 generation. Activity was also inhibited at 0.5 mM for 14CO2 release from labeled glucose and at 1.0 mM for nitroblue tetrazolium-reduction.</td>
</tr>
<tr>
<td>Human</td>
<td>Leukocyte capillary migration inhibition assay.</td>
<td>8% inhibition with 0.5 ppm fluoride and 20% inhibition with 20 ppm fluoride.</td>
</tr>
<tr>
<td>Various</td>
<td>Evaluated signal transduction in cultured macrophages exposed to NaF with or without aluminum.</td>
<td>NaF reduced intracellular ATP concentrations, suppressed agonist-induced protein tyrosine phosphorylation and reactive oxygen species formation. There was in situ activation of nitrogen-activated protein kinase, phospholipase A2, and phosphatidylinositol-phospholipase C. Little or no effect on NaF-mediated enzyme action was observed when cells were treated with AlCl3 or deferoxamine.</td>
</tr>
<tr>
<td>Human</td>
<td>Cell migration assay and micropore filter assay used to assess effect of NaF on locomotion and chemotaxis of human blood leukocytes.</td>
<td>Significant reduction in chemotaxis and locomotion observed with 1 mM fluoride.</td>
</tr>
<tr>
<td>Human</td>
<td>Cultured neutrophils treated with fluoride.</td>
<td>Fluoride activated diacylglycerol generation and phospholipase D activity. Increased diradylglycerol mass, with kinetics similar to superoxide generation.</td>
</tr>
<tr>
<td>Human</td>
<td>Electropermeabilized neutrophils treated with fluoride.</td>
<td>O2 production was increased by electropermeabilization. That effect was antagonized by GDP[β-S], required Mg2+, and was blocked by staurosporine and H-7.</td>
</tr>
<tr>
<td>Human</td>
<td>Adherence assay of PMNs cultured with 0.0625-4.0 µM with or without autologous serum.</td>
<td>No effect in the absence of serum. With serum, adherence significantly decreased at 0.5 µM. Decrease was 1.1% at 0.125 µM and 32.7% at 1.5 µM.</td>
</tr>
</tbody>
</table>
### TABLE 9-4 Effects of Fluoride on Immune System Cells

<table>
<thead>
<tr>
<th>Application/Proposed Mechanisms</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition was primarily due to suppression of nonoxidative glucose metabolism. Peak effect was at 20 mM, a lethal dose to the cells.</td>
<td></td>
<td>Gabler and Leong 1979</td>
</tr>
<tr>
<td>Effect at 0.5 ppm fluoride likely not significant. 20 ppm fluoride is 100 times higher than serum fluoride concentrations expected if 1.5 L of 4 ppm fluoride in water is consumed.</td>
<td></td>
<td>Gibson 1992</td>
</tr>
<tr>
<td>Authors suggest that some of the pleiotropic effects of NaF in intact cells might be due to depletion of ATP and not by G-protein activation.</td>
<td></td>
<td>Goldman et al. 1995</td>
</tr>
<tr>
<td>1 mM fluoride is a high concentration relative to blood fluoride, but such a concentration might be possible within the Haversian canal system of bone, restricting migration of leukocytes through bone.</td>
<td></td>
<td>Wilkinson 1983</td>
</tr>
<tr>
<td>Data are consistent with the activation of phosphatidic acid and diglyceride generation by both phospholipase D-dependent and independent mechanisms.</td>
<td></td>
<td>Olson et al. 1990</td>
</tr>
<tr>
<td>Supports the hypothesis that fluoride activates G protein, most likely Gp, by interacting with the nucleotide-binding site on the G α subunit.</td>
<td></td>
<td>Hartfield and Robinson 1990</td>
</tr>
<tr>
<td>Effect is not direct and is probably modulated by a seric factor.</td>
<td></td>
<td>Gomez-Ubric et al. 1992</td>
</tr>
<tr>
<td>Concentrations of fluoride tested are similar to those found in blood.</td>
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<tr>
<td>Species</td>
<td>Study</td>
<td>Findings</td>
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</tr>
<tr>
<td>Human</td>
<td>Promyelocytic HL-60 cells treated with 0.5 mM NaF for 0-4 days.</td>
<td>Cell proliferation was inhibited by NaF and was augmented by the addition of 1,25-dihydroxyvitamin D3. Other observations were changes in cellular morphology, increased cellular adhesion to plastic, reduced nuclear/cytoplasmic ratio, and increased cellular expression of chloroacetate esterase. No effect on cellular nonspecific esterase activity.</td>
</tr>
<tr>
<td>Human</td>
<td>Blood lymphocytes incubated with NaF at 0.31, 0.62, or 1.2 mM.</td>
<td>NaF augmented lymphocyte response to a mitogen (PHA) or a specific antigen (morbilli antigen from infected cells). Simultaneous incubation of NaF at 0.62 mM with PHA significantly increased cytokine INF-γ release from activated T and/or NK cells compared with treatment with PHA alone (P &lt; 0.01).</td>
</tr>
<tr>
<td>Human</td>
<td>CD34+ cells isolated from umbilical cord blood were incubated with 1, 10, and 50 mM NaF for 30 and 120 minutes.</td>
<td>At 10 and 50 mM NaF, there was damage to CFU-GM and significantly decreased cloning potential of these cells. Growth of BFU-E was also inhibited.</td>
</tr>
<tr>
<td>Rat</td>
<td>Liver macrophages treated with fluoride.</td>
<td>Arachidonic acid and prostaglandins were released (required extracellular calcium), but there was no formation of inositol phosphates or superoxide. Those effects were inhibited by staurosporine and phorbol ester. Protein kinase C was translocated from the cytosol to membranes.</td>
</tr>
<tr>
<td>Mouse</td>
<td>Cultured lymphocytes treated with NaF and AlCl3.</td>
<td>With NaF, there was a breakdown of polyphosphoinositides, decreased production of phosphoinositols, increased cytosolic Ca2+, and start of phosphorylation of the T-cell receptor. Effects were potentiated by addition of AlCl3.</td>
</tr>
<tr>
<td>Mouse</td>
<td>Bone marrow progenitor cells cultured with 0.1-0.5 mM NaF.</td>
<td>Upregulation in the activities of intracellular enzymes (LDH, β-glucuronidase, acid phosphatase), cellular reduction of nitroblue tetrazolium, and nitric oxide production.</td>
</tr>
<tr>
<td>Application/Proposed Mechanisms</td>
<td>Comments</td>
<td>Reference</td>
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<tr>
<td>NaF stimulates the early stages of HL-60 differentiation toward a granulocyte-like cell. 1,25-Dihydroxyvitamin D3 acts as a cofactor with NaF, primarily through interaction with an endogenous NaF-induced cyclooxygenase product(s), possibly PGE2.</td>
<td>Authors concluded that NaF’s effect on INF-γ release during an immune response might be one of the primary ways that fluoride ion influences the immune system.</td>
<td>Kawase et al. 1996</td>
</tr>
<tr>
<td>Calcium-dependent protein kinase C appears to be involved in fluoride’s action on liver macrophages.</td>
<td></td>
<td>Loftenius et al. 1999</td>
</tr>
<tr>
<td>The active moiety is AlF₄⁻. AlF₄⁻-induced effects were insensitive to cyclic adenosine monophosphate.</td>
<td></td>
<td>Machalinski et al. 2000</td>
</tr>
<tr>
<td>The active moiety is AlF₄⁻. AlF₄⁻-induced effects were insensitive to cyclic adenosine monophosphate.</td>
<td></td>
<td>Schulze-Specking et al. 1991</td>
</tr>
<tr>
<td>Authors suggest that NaF induces early differentiation of bone marrow hemopoietic progenitor cells along the granulocytic pathway but not the monocytic pathway linked to osteoclast formation.</td>
<td></td>
<td>O'Shea et al. 1987</td>
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<td></td>
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<td>Oguro et al. 2003</td>
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continued
### TABLE 9-4 Continued

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>Transferrin before or after 9 months treatment with 10 mg/kg/day. Circulating anti-transferrin titers were measured during the 9 months. DNA and protein synthesis were determined by $[\text{H}]$thymidine and $[\text{C}]$leucine incorporation.</td>
<td>NaF inhibited antibody formation and had a threshold of 0.78 ppm in circulation. DNA and protein synthesis were also inhibited.</td>
</tr>
<tr>
<td>Rat</td>
<td>Sensitization assay performed with rats administered 5 mL of a 100-mmol solution of NaF twice a week for 2-3 weeks and given ovalbumin in drinking water.</td>
<td>Significant increase in surface immunoglobulin expression on lymphocytes from the Peyer’s patches and mesenteric lymph nodes.</td>
</tr>
<tr>
<td>Rat</td>
<td>0.1, 0.2, and 0.4 mg of fluoride administered intratracheally.</td>
<td>Significant PMN-leukocyte infiltration in the lungs observed 24 hours after treatment with 0.2 and 0.4 mg. mRNA of chemokines and proinflammatory cytokines was increased. Increased adhesion of PMNs to plastic dish.</td>
</tr>
<tr>
<td>Mouse</td>
<td>Antibacterial defense mechanisms and lung damage were assessed in mice exposed to 2, 5, 10 mg/m$^3$ of a fluoride aerosol in an inhalation chamber for 4 hours per day for 14 days.</td>
<td>Suppression of pulmonary bactericidal activity against <em>Staphylococcus aureus</em> at 5 and 10 mg/m$^3$. Significant decrease in the number of alveolar macrophages in bronchoalveolar lavage fluid at 10 mg/m$^3$ in mice not bacterially challenged. Significant increase in PMNs and lymphocytes at 10 mg/m$^3$.</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** BFU-E, burst forming unit of erythrocytes; CFU-GM, colony-forming unit of granulocyte-macrophages; GDP[$\beta$-$S$], guanosine 5’-[\beta-thio]diphosphate; INF-$\gamma$, interferon $\gamma$; LDH, lactate dehydrogenase; PGE2, prostaglandin E; PHA, phytohemaggultinin; PMN, polymorphonuclear leukocyte.
### Species Study Findings Application/Proposed Mechanisms Comments Reference

| Antibody formation appears to be inhibited because of the decrease in lymphocyte proliferation and inhibition of protein synthetic ability of immunocytes. | General inhibition of metabolic function. | Jain and Susheela 1987 |
| Microulcerations of the gastric mucosa. | Authors note that the concentrations tested were within the range that could be inadvertently ingested by infants/children or adults from fluoride supplements or gels. | S. Hirano et al. 1999 |
| Authors concluded that inhalation of fluoride can cause cellular alterations in the lung that diminish the ability to respond to infectious bacteria. | | Yamamoto et al. 2001 |
in test animals and in vitro test systems. For example, a few studies suggest that fluoride might be associated with kidney stone formation, while other studies suggest that it might inhibit stone formation. Some effects on liver enzymes have been observed in studies of osteoporosis patients treated with fluoride, but the available data are not sufficient to draw any conclusions about potential risks from low-level long-term exposures. Little data is available on immunologic parameters in human subjects exposed to fluoride from drinking water or osteoporosis therapy, but in vitro and animal data suggest the need for more research in this area.

As noted earlier in Chapters 2 and 3, several subpopulations are likely to be susceptible to the effects of fluoride from exposure and pharmacokinetic standpoints. With regard to the end points covered in this chapter, it is important to consider subpopulations that accumulate large concentrations of fluoride in their bones (e.g., renal patients). When bone turnover occurs, the potential exists for immune system cells and stem cells to be exposed to concentrations of fluoride in the interstitial fluids of bone that are higher than would be found in serum. From an immunologic standpoint, individuals who are immunocompromised (e.g., AIDS, transplant, and bone-marrow-replacement patients) could be at greater risk of the immunologic effects of fluoride.

**RECOMMENDATIONS**

**Gastric Effects**

- Studies are needed to evaluate gastric responses to fluoride from natural sources at concentrations up to 4 mg/L and from artificial sources. Data on both types of exposures would help to distinguish between the effects of water fluoridation chemicals and natural fluoride. Consideration should be given to identifying groups that might be more susceptible to the gastric effects of fluoride.
- The influence of fluoride and other minerals, such as calcium and magnesium, present in water sources containing natural concentrations of fluoride up to 4 mg/L on gastric responses should be carefully measured.

**Renal and Hepatic Effects**

- Rigorous epidemiologic studies should be carried out in North America to determine whether fluoride in drinking water at 4 mg/L is associated with an increased incidence of kidney stones. There is a particular need to study patients with renal impairments.
- Additional studies should be carried out to determine the incidence, prevalence, and severity of renal osteodystrophy in patients with renal im-
pairments in areas where there is fluoride at up to 4 mg/L in the drinking water.

- The effect of low doses of fluoride on kidney and liver enzyme functions in humans needs to be carefully documented in communities exposed to different concentrations of fluoride in drinking water.

**Immune Response**

- Epidemiologic studies should be carried out to determine whether there is a higher prevalence of hypersensitivity reactions in areas where there is elevated fluoride in the drinking water. If evidence is found, hypersensitive subjects could then be selected to test, by means of double-blinded randomized clinical trials, which fluoride chemicals can cause hypersensitivity. In addition, studies could be conducted to determine what percentage of immunocompromised subjects have adverse reactions when exposed to fluoride in the range of 1-4 mg/L in drinking water.

- More research is needed on the immunotoxic effects of fluoride in animals and humans to determine if fluoride accumulation can influence immune function.

- It is paramount that careful biochemical studies be conducted to determine what fluoride concentrations occur in the bone and surrounding interstitial fluids from exposure to fluoride in drinking water at up to 4 mg/L, because bone marrow is the source of the progenitors that produce the immune system cells.
This chapter reviews research publications and relevant review articles published since the earlier NRC (1993) report and other relevant papers not included in that review, and also considers salient earlier papers. Evaluation of the plausibility and potential for carcinogenicity is based on human epidemiologic studies, laboratory animal lifetime bioassays, shorter-term genotoxicity tests, metabolism and pharmacokinetic data, and mechanistic information. Genotoxicity tests indicate the potential for fluoride to cause mutations, affect the structure of chromosomes and other genomic material; affect DNA replication, repair, and the cell cycle; and/or transform cultured cell lines to enable them to cause tumors when implanted into host animals. In interpreting the experimental studies and the consistency among disparate tests and systems, factors to be considered include the chemical form, concentrations, duration of exposure or application, vehicle or route of exposure, presence or absence of dose response, and information that each study provides about the potential stage of cancer development at which the chemical might operate. The degree of consistency of genotoxicity tests with the epidemiologic studies and whole animal bioassays on these points was evaluated.

**GENOTOXICITY**

Genotoxicity tests comprise in vitro and in vivo assays to assess the effects on DNA and chromosomal structure and/or function. The results of these assays serve as indicators of the potential interaction of chemicals with the genetic material. Changes in chromosomal or DNA structure or
function may be a step in the pathway to carcinogenesis. More often, they indicate interference with the normal duplication, function, and control of cell division and genetic activity that also might result in precancer or early neoplastic processes. Genotoxicity also encompasses the ability to cause germ cell and somatic cell mutations that cause malformations, disease, and other adverse health outcomes.

Many cell systems derived from various organisms have been used to assess genotoxicity of a large array of chemicals. In evaluating the applicability of the results of these tests to human risk from fluoride ingestion, some of the key parameters are the concentrations used in the assays compared with physiologic concentrations, the form and vehicle for fluoride exposure in the assay, and existing data on overall applicability of the various assays to risk in humans. Tennant (1987) and Tennant et al. (1987) concluded that the Salmonella reverse mutation assay was the best short-term genotoxicity assay available for predicting carcinogenicity in mammals. However, Parodi et al. (1991) reviewed the results of various genotoxicity tests in comparison with animal carcinogenicity studies, and found that in vitro cytogenetic tests, particularly sister-chromatid exchange tests (SCEs), were more predictive of carcinogenicity than the Salmonella reverse mutation assay. Tice et al. (1996) subsequently reviewed relative sensitivities of rodents and humans to genotoxic agents and concluded that humans are more than an order of magnitude more sensitive than rodents to most of the genotoxic agents they examined using the genetic activity profile database.

The available new genotoxicity studies of fluoride are detailed in Table 10-1. The most extensive and important additions to the genotoxicity literature on fluoride since 1993 are in vivo assays in human populations and, to a lesser extent, in vitro assays using human cell lines and in vivo experiments with rodents. These studies are discussed below.

**Gene Mutation**

Mutagenicity indicates direct action of a substance on DNA. Alterations in DNA suggest that the chemical has the potential to cause genetic effects as well as carcinogenic potential. In 1993, the existing literature did not indicate that fluoride posed a mutation hazard. The literature included assays with Salmonella (virtually all negative results), various mammalian cells lines (virtually all negative), and cultured human lymphocytes. Positive results in the human lymphocytes were seen at fluoride concentrations above 65 micrograms per milliliter (µg/mL) (parts per million [ppm]) and generally at more than 200 µg/mL, (much greater concentrations than those to which human cells in vivo typically would be exposed). No pertinent studies have been found since those reviewed in the 1993 NRC report. The committee interprets the weight of evidence from in vivo rodent studies to
TABLE 10-1 Summary of Recent Genotoxicity Studies of Fluoride

<table>
<thead>
<tr>
<th>Population or System/Method and Assay</th>
<th>Findings</th>
<th>Remarks</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>In vivo human studies</strong></td>
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<tr>
<td>Subjects (n = 746) with normal or inadequate nutrition living in regions of China with water concentrations of fluoride at 0.2, 1.0, or 4.8 mg/L. Assay: SCE in blood lymphocytes.</td>
<td>Subjects in the 4.8-mg/L region had lower average SCEs per cell.</td>
<td>Plasma and urine fluoride concentrations also measured; these were proportional to water concentrations.</td>
<td>Y. Li et al. 1995</td>
</tr>
<tr>
<td>Comparison of 100 residents of North Gujarat exposed to drinking water with fluoride at 1.95 to 2.2 mg/L with 21 subjects in Ahmedabad exposed at 0.6 to 1.0 mg/L. Assay: SCE in blood lymphocytes and cell cycle proliferative index.</td>
<td>SCE rate was significantly greater in subjects from North Gujarat, but there was no difference in the cell cycle proliferative index.</td>
<td>Insufficient documentation of subject ascertainment or control for potential demographic confounding.</td>
<td>Sheth et al. 1994</td>
</tr>
<tr>
<td>Phosphate fertilizer workers with inhalation exposure. Assay: chromosome aberrations, micronucleus, SCE.</td>
<td>Exposed workers had elevation in all cytogenetic outcomes tested.</td>
<td></td>
<td>Meng et al. 1995; Meng and Zhang 1997</td>
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<tr>
<td>Peripheral blood lymphocytes from inhabitants of the Hohhot region in inner Mongolia (n = 53 with fluorosis; n = 20 with no fluorosis) exposed to fluoride in drinking water at 4 to 15 mg/L compared with controls (n = 30) exposed to fluoride at &lt; 1 mg/L. Assay: SCE and micronucleus.</td>
<td>SCE: higher frequency in individuals with fluorosis (87% increase in SCEs), than no fluorosis (13% increase) compared with controls. Micronucleus: higher frequency in individuals with fluorosis (3.4-fold increase) than no fluorosis (1.8-fold increase) compared with controls.</td>
<td>Insufficient documentation of subject ascertainment or control for potential demographic confounding.</td>
<td>Wu and Wu 1995</td>
</tr>
<tr>
<td>Population or System/Method and Assay Findings</td>
<td>Remarks</td>
<td>References</td>
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<tr>
<td>Human populations with long-term residency in communities with water concentrations of fluoride at 0.2, 1.0, and 4.0 mg/L. Measured plasma and urine fluoride concentrations. Assay: SCE in blood lymphocyte.</td>
<td>SCEs higher in 4.0-mg/L community. Follow-up study in the 4.0-mg/L community comparing residents using well water (≤0.3 mg/L) and city water (4.0 mg/L) found no difference in SCE frequency between these two groups in the 4-mg/L town.</td>
<td>Jackson et al. 1997</td>
<td></td>
</tr>
<tr>
<td>Cultured peripheral blood lymphocytes from 7 female osteoporosis patients treated with disodium monofluorophosphate and NaF for 15 to 49 months (22.6 to 33.9 mg of fluoride/day). Measured serum fluoride. Assay: chromosomal aberration, micronuclei, cell cycle progression.</td>
<td>No cytogenetic effects compared with the matched controls.</td>
<td>Van Asten et al. 1998</td>
<td></td>
</tr>
<tr>
<td>Comparison of residents of South Gujarat exposed to drinking water with fluoride at 0.7 mg/L (control village) with residents exposed at 1.5 to 3.5 mg/L (3 villages). Assay: SCE in peripheral lymphocytes.</td>
<td>One of the high-fluoride villages had elevated SCEs. No difference was found between the other two and the control village. Insufficient documentation of subject ascertainment and demographic characteristics.</td>
<td>Joseph and Gadhia 2000</td>
<td></td>
</tr>
<tr>
<td>Case series in India of osteosarcoma (n = 20) compared with population distribution regarding bone tumor fluoride concentration and p53 mutations. Assay: p53 mutation and fluoride concentrations in tumor tissue.</td>
<td>Two (10%) cases had p53 mutants in osteosarcoma tissue, and those two had the highest bone tumor fluoride concentrations. Only patients undergoing prosthesis fitting at one hospital were selected; selection bias was possible. If replicated with systematic ascertainment, this design could indicate a mechanism for carcinogenic activity by fluoride.</td>
<td>Ramesh et al. 2001</td>
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TABLE 10-1 Continued

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<tr>
<th>Population or System/Method and Assay</th>
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<tbody>
<tr>
<td><strong>In vivo animal studies</strong></td>
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<tr>
<td>Mice (B6C3F1) exposed via drinking water for 6 weeks. Assay: micronuclei in peripheral red blood cells, chromosome aberrations in bone marrow.</td>
<td>No micronuclei increase in peripheral red blood cells, and no chromosome aberration increase in bone marrow. Bone concentrations of fluoride increased with dose to &gt;7,000 ppm.</td>
<td>Method addresses some of the conflicts in previous in vitro and in vivo studies.</td>
<td>Zeiger et al. 1994</td>
</tr>
<tr>
<td>Four Zucker rats, diabetic and nondiabetic males. Fluoride in water at 5 to 50 mg/L for 6 months. Assay: SCE.</td>
<td>No SCE elevation in any exposed subgroup.</td>
<td></td>
<td>Dunipace et al. 1996</td>
</tr>
<tr>
<td>Wistar rats exposed to NaF at 0, 7, and 100 mg/L in drinking water. Assay: single cell gel electrophoresis (Comet assay)</td>
<td>No increase in single-strand DNA damage.</td>
<td></td>
<td>Ribeiro et al. 2004a</td>
</tr>
<tr>
<td><strong>In vitro human studies</strong></td>
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<tr>
<td>Synchronized human diploid fibroblasts. Attempt to reconcile disparate methods of classifying aberrations (e.g., gaps). Assay: chromosome aberrations.</td>
<td>50 ppm NaF is lowest concentration inducing aberrations. Proposes mechanism of inhibition of DNA synthesis and repair.</td>
<td>Aardema and Tsutsui 1995</td>
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<tr>
<td>Study</td>
<td>Population or System/Method</td>
<td>Findings</td>
<td>Remarks</td>
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<tr>
<td>Mice (B6C3F1) exposed via drinking water for 6 weeks.</td>
<td>Measured fluoride concentrations in bone.</td>
<td>No increase in micronuclei and chromosome aberrations.</td>
<td>Bone fluoride concentrations increased with dose to &gt;7,000 ppm.</td>
</tr>
<tr>
<td>Four Zucker rats, diabetic and nondiabetic males.</td>
<td>Fluoride in water at 5 to 50 mg/L for 6 months.</td>
<td>No SCE increase in exposed subgroups.</td>
<td></td>
</tr>
<tr>
<td>Wistar rats exposed to NaF at 0, 7, and 100 mg/L in drinking water.</td>
<td>Assay: single-cell gel electrophoresis (Comet assay).</td>
<td>No increase in single-strand DNA damage.</td>
<td></td>
</tr>
<tr>
<td>In vitro human studies</td>
<td>Synchronized human diploid fibroblasts.</td>
<td>No clastogenicity.</td>
<td>50 ppm NaF induces clastogenicity.</td>
</tr>
<tr>
<td>Human lymphocytes from 50 individuals cultured in 10 to 30 ppm NaF.</td>
<td>Chromosomal aberration: 23% and 8% increased frequency of total aberrations at 20 and 30 ppm, respectively, but not at 10 ppm. SCE: no effects reported.</td>
<td></td>
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</tr>
<tr>
<td>Human embryo hepatocytes.</td>
<td>Treated with NaF at 40, 80, and 160 mg/L for 24 hours.</td>
<td>Dose-related increase in single-strand DNA damage.</td>
<td>Dose-related increase in lipid peroxidase, decrease in glutathione, and increase in the percentage of apoptotic cells.</td>
</tr>
<tr>
<td>Cell cultures of rodents, prosimians, apes, and humans.</td>
<td>Assay: chromosome aberration.</td>
<td>Clastogenicity of fluoride in great apes and human cells only at 42 to 252 ppm NaF.</td>
<td></td>
</tr>
<tr>
<td>BALB/c-3T3 mouse cells.</td>
<td>Assay: cell transformation.</td>
<td>1.2 to 4.6 mM (19 to 193 ppm) NaF negative for transformation.</td>
<td>Standard transformation assay modified to increase sensitivity.</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley) cultured bone marrow cells.</td>
<td>Assay: cytotoxicity and SCE.</td>
<td>Dose-response observed for cytotoxicity. No inhibition of cell proliferation. No effect on SCE.</td>
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### TABLE 10-1 Continued

<table>
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<tr>
<th>Population or System/Method and Assay</th>
<th>Findings</th>
<th>Remarks</th>
<th>References</th>
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<tbody>
<tr>
<td>Rat (Sprague-Dawley) cultured bone marrow cells. Treated with NaF and KF 0.1 to 100 µM for 12, 24, or 36 hours. Assay: chromosomal aberration and break.</td>
<td>Weak effects at 1.0 µM, NaF and KF. Effects slightly greater for KF than NaF.</td>
<td></td>
<td>Khalil 1995</td>
</tr>
<tr>
<td>Chinese hamster ovary cells. Treated with NaF at 7.28, 56, and 100 µg/mL for 3 hours. Assay: single cell gel electrophoresis (Comet assay)</td>
<td>No increase in single-strand DNA damage.</td>
<td></td>
<td>Ribeiro et al. 2004b</td>
</tr>
<tr>
<td>Rat (F344/N) vertebral cells. NaF treatments 1 to 3 days. Assay: chromosomal aberration.</td>
<td>Dose-related increases of chromosome aberrations at 0.5 and 1.0 mM for 24 and 48 hours. Potential target organ of NTP carcinogenicity studies that yielded osteosarcomas. Provides possible mechanism for carcinogenesis of vertebrae.</td>
<td></td>
<td>Mihashi and Tsutsui 1996</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** KF, potassium fluoride; NaF, sodium fluoride; NTP, National Toxicology Program.
indicate very low probability of a mutagenic risk for humans (NRC 1993; WHO 2002; ATSDR 2003).

Chromosomal Changes and DNA Damage

This section describes studies of fluoride’s effects on chromosomes and chromatids, formation of micronuclei, and DNA damage. Chromosomal alterations can include changes in chromosome number (aneuploidy) and aberrations of the chromosomes (before DNA synthesis) or chromatids (after DNA synthesis). (Nondisjunction or translocation of chromosome 21, producing Down’s syndrome, is discussed in Chapter 6 on Reproductive and Developmental Effects.) Classification of chromosome/chromatid aberrations has become standardized in recent years: some types of aberrations (e.g., chromatid gaps) are judged to be less important in evaluating effects on chromosomes than other major aberrations (e.g., breaks and translocations). SCE is not known to be on the causal pathway of any adverse health effects, but it is considered a generic indication of exposure to substances that can affect chromosomal structure, many of which are also carcinogens. The SCE assay is a helpful and widely used assay because of its greater sensitivity at lower concentrations than chromosome aberrations. Fewer cells need to be scored in order to establish with confidence whether an increase in SCEs has occurred in a specific test system.

Micronuclei are DNA-containing bodies derived from chromosomal material that is left behind during mitosis. Either a faulty mitotic process or chromosomal breaks can cause this phenomenon. Micronuclei can be visualized in nondividing cells. The relatively new “Comet assay” detects single-strand DNA damage in individual cells using microgel electrophoresis.

Effects on cell survival (cytotoxicity) and effects on cell division are commonly investigated and reported in the course of conducting in vitro cytogenetic studies, and they are included in the summary below.

Human Cells In Vitro

Interpreting the health significance of observed cytogenetic effects on human cells in culture depends on the dose, timing of application relative to the point in the cell cycle, and type of cultured cells, among other factors. As of the 1993 NRC report, the existing data of this type were inconsistent regarding the cytogenetic effects of fluorides. Since that time, Tsutsui et al. (1995) applied sodium fluoride (NaF) at or near concentrations found in water supplies (1 to 10 ppm, equivalent to 0.45 to 4.5 ppm fluoride ion) to diploid fibroblasts for up to 3 weeks and did not observe clastogenicity. Aardema and Tsutsui (1995) using a similar cell system found aberrations only above 50 ppm. The cell phases at which these effects were observed
suggested that the underlying mechanism of the chromosomal aberrations might be interference by fluoride with DNA synthesis and repair. In human diploid IMR90 cells, Oguro et al. (1995) observed clastogenicity only above 5 ppm NaF after short- and long-term applications. Gadhia and Joseph (1997) noted that 20 and 30 ppm NaF, but not 10 ppm, caused aberrations. No effects on SCEs were seen in their study. Recently, Wang et al. (2004) used the Comet assay to study genotoxicity in human embryo hepatocytes after treatment with NaF. They observed a dose-related increase in single-strand DNA damage at concentrations of 40, 80, and 160 mg/L.

Other Mammalian Systems In Vitro

Previous studies with a wide variety of test systems found cytogenetic effects in some but not all systems used (NRC 1993; WHO 2002; ATSDR 2003).

Recent studies with in vitro rodent systems include those by Khalil and Da’dara (1994) and Khalil (1995). They evaluated effects on cultured bone marrow cells of Sprague-Dawley rats after exposure to NaF or potassium fluoride (KF) at concentrations ranging from 0.1 µM to 0.1 mM (up to 2 ppm fluoride) for 12 to 36 hours. They did not observe increased SCE levels at any concentration, although there was dose-dependent cytotoxicity. Both NaF and KF induced chromosomal aberrations in a dose-dependent manner between 0.1 and 100 µM. Mihashi and Tsutsui (1996) studied effects on cultured vertebral cells of F344/N rats after 1 to 3 days of 9 to 18 ppm NaF treatment and found dose-dependent increases in chromosomal aberrations based on time and concentrations. Kishi and Ishida (1993) compared activity of NaF on chromosome aberrations for a series of cell lines from rodents, prosimians, great apes, and humans. Clastogenicity by 42 to 252 ppm NaF was seen only in the great ape and human cell lines. Their work thus indicates a greater sensitivity to fluoride in human than in rodent cells. In an older study not included in the NRC (1993) report, Jagiello and Lin (1974) reported that in vitro exposure of oocytes to NaF disrupted meiotic anaphase of ewes and cows but not of mice. The effective doses were the same order of magnitude as those reported by NRC in 1993 to cause chromosome aberrations in human lymphocytes. In vivo tests performed only in mice indicated that fluoride was not genotoxic, even at high doses. Ribeiro et al. (2004b) used the Comet assay to assess effects of NaF on Chinese hamster ovary cells in vitro. No damage was observed at concentrations of up to 100 µg/mL.
Rodent Systems In Vivo

Zeiger et al. (1994) administered NaF in drinking water for 6 weeks to B6C3F1 mice and assayed micronuclei and chromosome aberration occurrences. They observed no increases over unexposed controls. Similarly, Dunipace et al. (1996) exposed diabetic and nondiabetic Zucker male rats to fluoride concentrations up to 50 mg/L in water for up to 6 months. They found no increase in the rate of SCEs for any test group.

Ribeiro et al. (2004a) exposed Wistar rats to NaF at 7 and 100 mg/L in drinking water for 6 weeks. Comet assays of peripheral blood, oral mucosa, and brain cells in vivo showed no increase in single-strand DNA damage.

Nonmammalian Systems In Vivo

Previous work on nonmammalian systems was sparse but did not indicate consistent cytogenetic effects. No new relevant studies have been reported.

Human Cells In Vivo

The NRC 1993 report noted the absence of human in vivo genotoxicity studies. Since 1993, important contributions to the evaluation of genotoxicity of fluoride have been in the area of cytogenetic studies of human populations exposed via diverse routes to various fluorides. Studies of human populations have the advantage of evaluating pertinent concentrations in a physiologically relevant context, despite the limitations inherent in all epidemiologic observational studies of not controlling for all factors that might be pertinent. Relevant studies are summarized below according to route of exposure.

Ingestion Route

The most well-documented in vivo human study published was that of Y. Li et al. (1995), who assayed the fluoride concentrations in water, plasma, and urine in more than 700 individuals. Six groups of 120 subjects resided in different locales with average naturally occurring fluoride concentrations in drinking water varying between 0.2 and 5 mg/L. They observed that, although plasma and urine fluoride concentrations varied with water concentrations, the groups of subjects living in the regions with higher concentrations of fluoride had lower average SCEs per cell. The study controlled for the nutritional status of the subjects. Subsequently, Jackson et al. (1997) compared SCE occurrence in lymphocytes of residents of communities with water fluoride concentrations of 0.2, 1, and 4 mg/L. Residents of the 4-mg/L...
The fluoride community had more average SCEs. In a follow-up study, there was no difference between the mean SCE level of a subsample of residents using the 4-mg/L community water and another sample of residents using 0.3-mg/L well water.

The following three less-well-documented studies reported associations between cytogenetic effects and residence in areas with high natural fluoride concentrations in drinking water. Sheth et al. (1994) published a preliminary investigation of SCEs in 100 residents of Gujarat, India, with fluorosis and 21 unaffected controls. They reported higher SCE rates among the fluorosis cases as well as higher fluoride concentrations in the cases’ water. The design of this study was seriously deficient, particularly because of the possibility of selection bias; cases and controls were recruited from different areas (cases were from areas with higher naturally occurring fluoride in drinking water). Additionally, clinical criteria for case definition were not adequately documented. Wu and Wu (1995) examined peripheral blood lymphocytes in a small series (n = 53) of residents in a high-natural-fluoride area (4 to 15 mg/L) and 30 control residents from a low-fluoride area (<1 mg/L) of Inner Mongolia. SCEs and micronuclei were more frequent only among subjects with fluorosis and not among those with higher exposures who did not exhibit fluorosis. The report had a dearth of information on subject selection and on control of potential confounding factors. Joseph and Gadhia (2000) later compared residents of three villages that had drinking water concentrations of fluoride at 1.6 to 3.5 mg/L with residents of Gujarat, India, where there is fluoride in residential drinking water at 0.7 mg/L. Chromosome aberrations were strongly elevated in residents of all three of the villages. SCE rates were elevated only in residents of one of those, and the same village’s residents also demonstrated higher chromosome aberrations in mitomycin-C-treated lymphocytes. Only 14 individuals were tested from each village, and the method of subject selection was not reported.

Van Asten et al. (1998) found no cytogenetic effects (aberrations, micronuclei, or cell cycle progression) on cultured lymphocytes in women who had been treated with fluoride (22.6 to 33.9 mg/day) for osteoporosis for 1 to 4 years.

**Inhalation and/or Dermal Routes**

Two articles published by Meng et al. (1995) and Meng and Zhang (1997) described cytogenetic assays in phosphate fertilizer workers. Inhalation of fluoride is the principal chemical exposure in these plants. The air concentrations of fluoride ranged from 0.5 to 0.8 mg/m³ at the time of the study. Chromosomal aberrations, micronuclei, and SCEs were all elevated in exposed workers. The length of exposure did not show a dose-dependent relationship with these cytogenetic effects; those working at the plant for 5
to 10 years had the greatest effect compared with those working for more than 10 years or less than 5 years. It is not clear, however, whether length of employment is a pertinent exposure metric concerning the plausibility of cytogenetic risk of fluoride for this cohort.

Cell Transformation

Cell transformation is the conversion of normal cells to neoplastic cells in vitro. In the 1993 NRC report, the positive transformation results reported were largely in Syrian hamster embryo (SHE) cells for which results cannot be extrapolated to human systems or other cell types (NRC 1993). However, in the one study that included an additional system, BALB/3T3 mouse cells (Lasne et al. 1988), transformation was observed with NaF at 25 to 50 ppm primarily in a promotional model with a known carcinogen as an initiator, suggesting this mechanism for a potential carcinogenic effect of fluoride. Since that time, the only additional pertinent publication is by Matthews et al. (1993), who also used a BALB/3T3 system with assay modifications to increase sensitivity. They tested numerous chemicals including 1.2 to 4.6 mM NaF (19 to 193 ppm), which did not exhibit transformational activity according to their criteria.

DNA Synthesis and Repair

A report from India (Ramesh et al. 2001) described a case series of 20 osteosarcoma patients of which the two with the highest fluoride concentrations in their tumor tissue had mutations of the tumor-suppressor gene \( p53 \) and the others did not. The normal \( p53 \) allele appears to protect cells from some mutagenic exposures by enhancing DNA repair mechanisms, and the dominant, null mutation is often found in soft tissue and osteosarcomas (Wadayama et al. 1993; Hung and Anderson 1997; Semenza and Weasel 1997). However, it should be noted that the fluoride concentration reported in the tumors with \( p53 \) mutations (i.e., 64,000 and 89,000 mg/kg versus 1,000-27,000 mg/kg in the remaining patients) exceed the theoretical maximum fluoride concentration of 37,700 mg/kg in bone (see Chapter 3). No data were presented regarding drinking water concentrations or other sources of fluoride exposures for those patients. The observations in this small case series are consistent with a role of fluoride in \( p53 \) mutations that could influence the development of osteosarcoma.

No other studies on DNA synthesis or repair have been found since those reviewed in the 1993 NRC report. Previous results were inconsistent but suggested that a mechanism for genotoxicity might be secondary to inhibition of protein or DNA synthesis (NRC 1993).
Update on Genotoxicity Conclusions and Recommendations of NRC (1993)

Overall, the results in in vitro systems summarized above are inconsistent and do not strongly indicate the presence or absence of genotoxic potential for fluoride. In 1993, NRC concluded that the existing genotoxicity data probably were not of “genetic significance.” There were no specific 1993 NRC recommendations regarding genotoxicity studies, although the report did mention the dearth of human in vivo assays. The more recent literature on in vitro assays does not resolve the overall inconsistencies in the earlier literature.

The human population in vivo studies published during the past 10 years comprise a new body of data that might be pertinent to evaluating the genotoxic potential of fluoride; those population studies by definition integrate the pharmacokinetic contexts and actual cell environment parameters resulting from external exposures, whether via water or other environmental media. However, the inconsistencies in the results of these in vivo studies do not enable a straightforward evaluation of fluoride’s practical genotoxic potential in humans.

CARCINOGENICITY

Animal Cancer Studies

Two studies were judged in the 1993 NRC review as adequate for the consideration of carcinogenic evidence in animals: an NTP study in F344/N rats and B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice (NTP 1990) and studies in Sprague-Dawley rats (Maurer et al. 1990) and in CD-1 mice (Maurer et al. 1993). The latter study in CD-1 mice was in press at the time of the NRC (1993) review. Two neoplasms were noted in the weight-of-evidence discussion:

1. Positive dose-related increase in the trend ($P = 0.027$) of osteosarcoma in male F344/N rats through drinking water route of exposure (NTP 1990)
2. Positive increase of osteoma in male and female CD-1 mice through dietary inclusion exposure (Maurer et al. 1993).

The review concluded that “the collective data from the rodent fluoride toxicological studies do not present convincing evidence of an association between fluoride and increased occurrence of bone cancer in animals” (NRC 1993).

Since the publication of the 1993 NRC review, the discussion on the uncertainties and overall weight of evidence in animals was further ex-
panded (WHO 2002; ATSDR 2003). Most of the uncertainties had already been highlighted in the NTP study. However, the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans. The key issues are presented in this section. In addition, the committee found another NTP study that adds to the database on fluoride.

NTP Studies

In the chronic bioassays by NTP (1990), F344/N rats and B₆C₃F₁ mice were administered NaF in drinking water at of 25, 100, and 175 mg/L, 7 days per week for 2 years. A summary of the neoplasms found is presented in Table 10-2. Osteosarcomas of the bone were found in male rats (1 of 50 and 3 of 80 in the mid- and high-dose groups, respectively) but not in female rats or in mice. An additional male rat in the 175-mg/L group had osteosarcoma of the subcutaneous tissue. Rats and mice exhibited tooth discoloration, and male rats had tooth deformities and attrition.

To adequately assess the oncogenicity of a chemical, it is important that the dose range used in the study is sufficiently high, attaining the maximum tolerated dose (MTD) or minimally toxic dose. There was a lack of significant toxicity of NaF in F344/N rats and B₆C₃F₁ mice, which suggested that higher doses could be tolerated (NTP 1990). Thus, it can be argued that the oncogenicity of fluoride in drinking water cannot be fully assessed on the basis of this study. Although this could be the case for the study in mice, given that rats at the high dose already showed various tooth abnormalities, higher-dose treatment might interfere with the rat's ability to eat (NTP 1990).

Increased incidence of osteosarcoma was reported in the high-dose male rats (Table 10-2). Opinion differs regarding the appropriateness of including the one case of extraskeletal osteosarcoma in the remaining incidence of osteosarcomas found in vertebrae and humerus (NTP 1990; PHS 1991; ATSDR 2003). The incidence from all sites gives stronger statistical significance than from the bone alone, lowering the P value from \( P = 0.027 \) to \( P = 0.01 \) for dose-related trend (logistic regression test) and from \( P = 0.099 \) to \( P = 0.057 \) for the pair-wise comparison with the controls (NTP 1990). A comparison with the historical control series was also presented, although its significance was compromised because of the higher fluoride in the standard diet used for the historical data, and because the radiograph used in the fluoride drinking water study was not routinely used in bone examinations (NTP 1990). Osteosarcoma is a rare tumor in rats. More recent historical data from Haseman et al. (1998) became available after the data from Haseman et al. (1985) that were used for the evaluation in the fluoride drinking water study. The data published in 1985 included studies
TABLE 10-2 Incidence of Neoplasms Highlighted in the NTP and Maurer et al. Studies

<table>
<thead>
<tr>
<th>NaF in Drinking Water (NTP 1990)</th>
<th>Site of Neoplasm</th>
<th>Control</th>
<th>25 mg/L</th>
<th>100 mg/L</th>
<th>175 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male F344/N rats</td>
<td>Osteosarcoma: bone</td>
<td>0/80 (0%)+</td>
<td>0/51 (0%)</td>
<td>1/50 (2%)</td>
<td>3/80 (4%)</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma: all sites</td>
<td>0/80 (0%)++</td>
<td>0/51 (0%)</td>
<td>1/50 (2%)</td>
<td>4/80 (5%)</td>
</tr>
<tr>
<td></td>
<td>Oral cavity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0/80 (0%)</td>
<td>1/51 (2%)</td>
<td>2/50 (4%)</td>
<td>3/80 (4%)</td>
</tr>
<tr>
<td></td>
<td>Thyroid&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/80 (1%)+</td>
<td>1/51 (2%)</td>
<td>1/50 (2%)</td>
<td>4/80 (5%)</td>
</tr>
<tr>
<td>Female F344/N rats</td>
<td>Osteosarcoma: bone</td>
<td>0/80 (0%)</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
<td>0/81 (0%)</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma: all sites</td>
<td>0/80 (0%)</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
<td>0/81 (0%)</td>
</tr>
<tr>
<td></td>
<td>Oral cavity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/80 (1%)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
<td>3/80 (4%)</td>
</tr>
<tr>
<td></td>
<td>Thyroid&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/80 (3%)</td>
<td>0/50 (0%)</td>
<td>2/50 (4%)</td>
<td>2/81 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NaF in Drinking Water (NTP 1992)</th>
<th>Site of Neoplasm</th>
<th>Control</th>
<th>250 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male F344 rats</td>
<td>Osteosarcoma: bone</td>
<td>2/49 (4%)</td>
<td>1/49 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NaF in Diet (Maurer et al. 1993)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Site of neoplasm</th>
<th>Control</th>
<th>4 mg/kg/day</th>
<th>10 mg/kg/day</th>
<th>25 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male CD-1 mice</td>
<td>Osteoma: bone</td>
<td>1/50 (2%)</td>
<td>0/42 (0%)</td>
<td>2/44 (5%)</td>
<td>13/50 (26%)***</td>
</tr>
<tr>
<td>Female CD-1 mice</td>
<td>Osteoma: bone</td>
<td>2/50 (3%)</td>
<td>4/42 (10%)</td>
<td>2/44 (5%)</td>
<td>13/50 (26%)**</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistical significance: trend test at $P \leq 0.05$ (+); $P \leq 0.01$ (++). Fisher pair-wise comparison at $P \leq 0.01$ (**); $P \leq 0.001$ (***)). The average daily dose for the male rat control, 25-, 100-, or 175-mg/L group was 0.2, 0.8, 2.5, or 4.1 mg of fluoride/kg/day.

<sup>b</sup>Included squamous papillomas and squamous cell carcinomas in oral mucosa, tongue, or pharynx.

<sup>c</sup>Follicular cell adenomas or carcinomas.

<sup>d</sup>The given dose is in NaF. Adjusted for the 45% weight difference between fluoride and NaF, the dose for the treatment group was 1.8, 4.5, or 11.3 mg of fluoride/kg/day. Fluoride intake for the control mice was 0.9 mg of NaF/kg/day (0.4 mg of fluoride/kg/day) for the males and 1.1 mg of NaF/kg/day (0.5 mg of fluoride/kg/day) for the females.

completed between 1979 and 1984, whereas the data published in 1998 were a 7-year collection up to January 1997. The 1990-1997 data showed a lower historical incidence of 0.1% (range 0% to 2%) each for bone and for all skin sites (Haseman et al. 1998). Ideally, historical data closer to the time frame of the bioassay of comparison would be more pertinent. On the basis of the 1990-1997 data, the incidence of osteosarcoma at the high dose appeared to exceed the historical range. Nevertheless, the same issues in making comparisons with historical data remain—historical control animals were not fed a low-fluoride diet and their bones were probably not examined with radiograph.
Additionally highlighted in the NTP report were the oral cavity squamous papillomas and squamous cell carcinomas (oral mucosa, tongue, pharynx) in male and female rats and thyroid follicular cell adenomas and carcinomas in high-dose male rats (Table 10-2). Both showed some increase with dose. The incidence at the high dose exceeded the historical control but stayed within the high end of the historical range and was not statistically significant from the concurrent control. The marginal increase in these neoplasms might not provide additional weight to the overall evidence of oncogenicity, but their occurrence could serve as an additional guide for epidemiologic studies.

Among the other tumor sites and types highlighted in the NTP report as not statistically and biologically significant was the hepatocellular neoplasm (adenoma, carcinoma, hepatoblastoma, and hepatocellular angiocarcinoma) in male and female mice (NTP 1990). Among these neoplasms, five in male and four in female treatment groups (unspecified) were reported by the contract laboratory as hepatocellular angiocarcinoma (NTP 1990). All but one in the females were reclassified into hepatoblastoma by the NTP pathology working group (NTP 1990). The incidence of these rare neoplasms not seen in the concurrent controls (historical hepatoblastoma of 0/2,197 in male mice and 1/2,202 in female mice) was judged as not significant when grouped with the more common hepatocellular adenomas and carcinomas (NTP 1990).

Another study conducted by NTP (1992, released in 2005) that bears on the carcinogenicity evaluation of fluoride is one that investigated the interaction of fluoride on the development of osteosarcoma induced by ionizing radiation. Pertinent to the committee’s evaluation was a group of nonirradiated male F344 rats that were administered NaF at 250 mg/L in drinking water for two years. Of the 49 rats per group that were examined, osteosarcoma of the bone occurred in one NaF treated rats and two non-irradiated controls. Thus, the results did not show an increase of osteosarcoma with NaF. However, this single data point does not have sufficient statistical power for detecting low level effects and rendered its observed results statistically compatible with those from the NTP (1990) bioassay. It is noteworthy that the study had the unexpected result that none of the irradiated animals developed osteosarcoma.

Maurer et al. Studies

Maurer et al. (1990, 1993) fed Sprague-Dawley rats and CD-1 mice diets containing NaF at doses of 4, 10, and 25 mg/kg/day for up to 99 weeks (rats) or 97 weeks (mice). Evidence of toxicity included decreased weight gain in the high-dose rats and non-neoplastic changes of the teeth (rats and mice), bones (rats and mice), joints (mice), and stomach (rats). In rats, no incidence of preneoplastic or neoplastic lesions was significantly different
from that in controls. In mice, increased incidence of osteomas (noncancerous bone tumors) was reported (Table 10-2).

The many limitations of the studies in rats and mice were identified in the earlier NRC (1993) review. The histopathologic examination of bones was not performed for all test animals (PHS 1991; WHO 2002; ATSDR 2003). Data on neoplasm were reported only for the bone and stomach. Moreover, based on the joint review by the Carcinogenicity Assessment Committee, Center for Drug Evaluation and Research, and U.S. Food and Drug Administration, questions were raised about the adequacy of the histopathologic examinations (PHS 1991). In the original report, fibroblastic sarcoma with areas of osteoid formation, chordoma, and chondroma were found in the males and osteosarcoma and chondroma were found in the females. However, the joint review discovered additional osteosarcoma in males and females. Collectively, those discrepancies called into question the weight of this negative study in the overall weight-of-evidence consideration (PHS 1991).

In the study with CD-1 mice, increased osteoma was reported in males and females at the high dose (Maurer et al. 1993). The authors reported that retrovirus infection in mice from all test groups might have confounded the occurrence of osteoma. The earlier NRC (1993) review considered the impact of the infection and concluded that the fluoride exposure was the most obvious cause for the increase in osteoma. However, based on the view of the Armed Forces Institute of Pathology (AFIP) that the osteomas were more reminiscent of a hyperplastic lesion, NRC (1993) concluded that their relevance to humans was questionable.

Human Cancer Studies

General Issues

Inherent difficulties for conducting epidemiologic studies of the cancer potential of fluoride and drinking water are similar to those challenges of studying most environmental chemicals. The limitations severely affect the possibility of identifying relatively small effects on cancer incidence and, especially, cancer mortality. Chief among them are the latency of cancer diagnosis after exposure to causal factors, typically spanning more than 10 years and often reaching 30 years. Migrations into and out of fluoridated areas often lead to misclassification of exposures when individual residency histories are not known. The diversity of cancers, comprising many different diseases rather than a single entity, necessitates evaluating each type of cancer separately rather than all cancers combined. Even so, there are few cancers for which specific environmental chemicals impart high attributable risks for the overall population or even among exposed populations.
The basic criteria for evaluating studies are appropriate methodology, potential selection and information biases, statistical power to detect real associations, appropriate time windows for assessing exposures and potential effects, and control for potential confounding by sociodemographic and other factors. In addition, sufficiently specific end points (types of cancer) and adequate exposure estimation are necessary for any epidemiologic study of fluoride and cancer to be informative for the committee’s task. A further issue is consideration of sensitive subpopulations based on a priori physiologic or previous epidemiologic data. Finally, it is necessary to apply biologic plausibility criteria and a weight-of-evidence approach to evaluate whether any observed associations should be interpreted as causal.

Many of the studies published before and since the 1993 NRC report are “ecologic studies.” In these designs, populations rather than individuals are the units of observation. A typical ecologic study regresses disease rates in different areas against average exposures. Such studies are usually less expensive and less time-consuming to conduct because the component data are already available. Incidence data are often very reliable if they are derived from high-quality population-based registries and census data. However, ecologic studies are often insensitive to small effects because of their design. The Agency for Toxic Substances and Disease Registry (ATSDR 2003) estimated that the ecologic studies performed to date for fluoride and cancer did not have sensitivities to detect less than 10% to 20% increases in cancer risk. Ecologic studies can be subject to large amounts of bias. Confounding factors and limited ability to control for such factors can be particularly serious problems (see Appendix C for a more detailed discussion of ecologic bias).

In semi-individual (partially ecologic) designs, individual-level information is collected for outcome and important variables, but exposure is assigned at the group level (e.g., based on residence or job title). Although such studies can share some characteristics of fully ecologic studies, they have much better ability to control confounding (see Appendix C).

Individual-based studies are composed of (1) case-control studies in which a group of people with a disease are compared with a sample of the population giving rise to the cases (controls) with regard to exposures that occurred before diagnosis, (2) cohort studies in which exposed and nonexposed people are followed forward in time and the disease experience of the two groups are compared, and (3) hybrids of these case-control and cohort designs. In environmental epidemiology, generally hundreds of subjects are required to detect with statistical significance any less than a twofold increase in risk of disease associated with a particular exposure. If an environmental agent is a weak carcinogen, with risks as low as 1 per 100,000 or 1 per 1,000,000 of those affected, it is extremely difficult to detect such effects by standard epidemiologic methods. This is particularly
true of cohort studies, which would need to enroll large numbers of subjects to detect differences between exposed and unexposed cohorts when the risks are low.

Epidemiology Data for Carcinogenicity of Fluoride

The weight of evidence for epidemiologic studies that NRC reviewed in 1993 did not indicate cancer risk to humans from fluoride exposure. However, the predominant methods used, particularly ecologic studies for which individual exposure histories could not be collected and confounding variables could not be controlled, were inadequate to rule out a weak effect. Some studies reported positive associations and some did not, but many of the studies were flawed in that adjustment for potential sociodemographic confounders was lacking or inadequate.

Epidemiologic studies published since the early 1990s and other pertinent studies not included in the 1993 NRC review are detailed in Table 10-3. The data are discussed below according to target sites for which associations with fluoride have been reported by at least one study.

Bone and Joint Cancers, Particularly Osteosarcoma

Osteosarcoma presents the greatest a priori plausibility as a potential cancer target site because of fluoride’s deposition in bone, the NTP animal study findings of borderline increased osteosarcomas in male rats, and the known mitogenic effect of fluoride on bone cells in culture (see Chapter 5). Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in nondividing states. Osteosarcoma is a rare disease, with an overall annual incidence rate of approximately 0.3 per 100,000 in the United States (Schottenfeld and Fraumeni 1996). The age of diagnosis is bimodal with peaks before age 20 and after age 50.

The incidence and mortality studies of osteosarcoma reviewed by NRC 1993 were ecologic or semi-ecologic in design. Their results were contradictory and inconclusive. The incidence studies of Hoover et al. (1991) at the National Cancer Institute observed that osteosarcoma rates in young males increased in the fluoridated areas compared with the nonfluoridated areas of two SEER registries they analyzed (Iowa and Seattle). However, the authors concluded that an association of fluoridation and osteosarcoma was not supported by the data because there was no linear trend of increased rate of osteosarcoma with the duration of fluoridation of the pertinent water supplies. The Hrudey et al. (1990) osteosarcoma incidence study in Alberta, Canada, and the Freni and Gaylor (1992) mortality analysis of bone cancer
**TABLE 10-3 Summary of Recent Studies of Fluoride and Cancer**

<table>
<thead>
<tr>
<th>Study Design &amp; Location</th>
<th>Observations</th>
<th>Findings</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Individual-based studies (cohort or case control)</em></td>
<td></td>
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<tr>
<td>Case-control study of pediatric osteosarcoma. NY State residents.</td>
<td>130 cases plus matched controls, patient and/or parent interviewed re residency history, fluoride ingestion sources, and other factors. 59 pairs of subjects were interviewed.</td>
<td>All data combined: odds ratios (ORs) for total fluoride ingestion decreased. ORs for water ingestion were elevated. Total fluoride protective for males. Reduced data for subjects (vs. parents) only: elevated ORs with dose response but wide confidence intervals.</td>
<td>Water ingestion alone not discussed by authors. No data or analysis of possible critical time window or latency. Paper contained some reversal of data columns in gender-specific tables and some misstatements regarding proportions of males and females with osteosarcoma. However, on the basis of information available to the committee, those specific errors do not appear to affect interpretation of this study.</td>
<td>Gelberg et al. 1995</td>
</tr>
<tr>
<td>Historical occupational cohort study of cryolite worker. SIRs. Denmark.</td>
<td>522 workers exposed.</td>
<td>Increased incidence or urinary bladder and respiratory cancers.</td>
<td>No smoking or drinking water data.</td>
<td>Grandjean et al. 1992; Grandjean and Olsen 2004</td>
</tr>
<tr>
<td>Case-control osteosarcoma analysis using public records only. Wisconsin.</td>
<td>167 cases and 989 cancer referents (brain, digestive system) from state cancer registry. Not interviewed.</td>
<td>No association with residential fluoridation, including ages 0 to 24. (Positive association with naturally occurring radiation in water.)</td>
<td>Lack of residential history via interview and use of cancer referents are limitations.</td>
<td>Moss et al. 1995</td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th>Study Design &amp; Location</th>
<th>Observations</th>
<th>Findings</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case control of osteosarcoma, age &lt;20 years</td>
<td>91 cases, 188 controls, interviewed on residency history and other fluoride exposures. Hospital-based.</td>
<td>Associations of exposures to fluoride at approximately 1 mg/L in water with osteosarcoma during ages 6 to 8, particularly for males.</td>
<td>Exploratory dissertation, multiple limitations in design, analysis, and presentation of findings.</td>
<td>Bassin 2001</td>
</tr>
<tr>
<td>Ecologic studies</td>
<td>49 cities or countries on 5 continents, classified as high or low cancer incidence. Where fluoride concentrations were unavailable, used data from neighboring area.</td>
<td>Inverse relationship between cancer rates and fluoridation reported $R = -0.75$. Latitude and temperature also analyzed, but not together as covariates.</td>
<td>Averaged male and female rates, and combined all cancers.</td>
<td>Steiner 2002</td>
</tr>
<tr>
<td>Ecologic analysis using proportions of populations with estimated fluoride concentrations $\geq 0.7$ mg/L. USA (6 cities, 3 states).</td>
<td>9 areas, 36 different sites of cancer, three 5-year periods. 15 years or 5 years (when different) coefficients and cancer incidence ratios. Used log-transformation of fluoride concentration and cancer rates.</td>
<td>Regression coefficient highest for females’ 1990 oral/digestive and male bone cancers.</td>
<td>Large number of comparisons. Cancer rates not shown. Rate distribution stated to be Poisson. Results presented selectively. Statistical methods flawed.</td>
<td>Takahashi et al. 2001</td>
</tr>
<tr>
<td>Mortality trends or uterine cancer before and after fluoridation terminated. Multiple regression. Okinawa, Japan.</td>
<td>20 of the 53 towns included. Controlled for sociodemographics. All fluoride concentrations below 0.4 mg/L.</td>
<td>Positive correlation of fluoridation with mortality rates. Mortality rates among the towns converged after fluoridation terminated.</td>
<td>Up to 13 years of exposure data combined. Hypothesis generated and data analyzed further in same population.</td>
<td>Tohyama 1996</td>
</tr>
</tbody>
</table>

**TABLE 10-3 Continued**
<table>
<thead>
<tr>
<th>Study Design &amp; Location</th>
<th>Observations</th>
<th>Findings</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case control of osteosarcoma, age &lt;20 years</td>
<td>U.S. multi-site</td>
<td>91 cases, 188 controls, interviewed on residency history and other fluoride exposures. Hospital-based.</td>
<td>Associations of exposures to fluoride at approximately 1 mg/L in water with osteosarcoma during ages 6 to 8, particularly for males. Exploratory dissertation, multiple limitations in design, analysis, and presentation of findings.</td>
</tr>
<tr>
<td>Ecologic studies</td>
<td>Ecologic, correlations of cancer incidence (combined) for fluoride concentrations. Worldwide.</td>
<td>49 cities or countries on 5 continents, classified as high or low cancer incidence. Where fluoride concentrations were unavailable, used data from neighboring area.</td>
<td>Inverse relationship between cancer rates and fluoridation reported $R = -0.75$. Latitude and temperature also analyzed, but not together as covariates. Averaged male and female rates, and combined all cancers.</td>
</tr>
<tr>
<td>Ecologic analysis using proportions of populations with estimated fluoride concentrations $\geq 0.7$ mg/L.</td>
<td>USA (6 cities, 3 states). 9 areas, 36 different sites of cancer, three 5-year periods. 15 years or 5 years (when different) coefficients and cancer incidence ratios. Used log-transformation of fluoride concentration and cancer rates.</td>
<td>Regression coefficient highest for females' 1990 oral/digestive and male bone cancers. Large number of comparisons. Cancer rates not shown. Rate distribution stated to be Poisson. Results presented selectively. Statistical methods flawed.</td>
<td></td>
</tr>
<tr>
<td>Mortality trends or uterine cancer before and after fluoridation terminated. Multiple regression.</td>
<td>Okinawa, Japan. 20 of the 53 towns included. Controlled for sociodemographics. All fluoride concentrations below 0.4 mg/L.</td>
<td>Positive correlation of fluoridation with mortality rates. Mortality rates among the towns converged after fluoridation terminated. Up to 13 years of exposure data combined. Hypothesis generated and data analyzed further in same population.</td>
<td></td>
</tr>
<tr>
<td>Comparison of cancer mortality rates for towns with high vs. low natural fluoride concentrations. Taiwan.</td>
<td>10 high and 10 low matched towns compared. Total populations exceeded 1 million. Rate ratios (SMRs) generated.</td>
<td>The only finding with 95% confidence interval excluding 1.0 = excess of bladder cancer in females. Also higher rate ratios in males for bone, females for uterus, colon, all sites; both genders.</td>
<td>Multiple comparisons. Hypothesis-generating. Controlled for urbanization and disinfection by-products. Osteosarcomas not distinguished from other bone cancers.</td>
</tr>
<tr>
<td>Comparison of cancer mortality rates for towns with high vs. low natural fluoride concentrations. Taiwan.</td>
<td>Incidence and mortality statistics; subtracted female from male osteosarcoma rates. Worldwide.</td>
<td>Used U.S. and NJ rates, among others.</td>
<td>Concluded that the difference between male and female rates between fluoridated and nonfluoridated areas indicates cancer associations.</td>
</tr>
<tr>
<td>Comparison of cancer mortality rates for towns with high vs. low natural fluoride concentrations. Taiwan.</td>
<td>Incidence and mortality statistics; subtracted female from male osteosarcoma rates. Worldwide.</td>
<td>Used U.S. and NJ rates, among others.</td>
<td>Concluded that the difference between male and female rates between fluoridated and nonfluoridated areas indicates cancer associations.</td>
</tr>
<tr>
<td>Comparison of cancer mortality rates for towns with high vs. low natural fluoride concentrations. Taiwan.</td>
<td>Incidence and mortality statistics; subtracted female from male osteosarcoma rates. Worldwide.</td>
<td>Used U.S. and NJ rates, among others.</td>
<td>Concluded that the difference between male and female rates between fluoridated and nonfluoridated areas indicates cancer associations.</td>
</tr>
<tr>
<td>Incidence and mortality statistics; subtracted female from male osteosarcoma rates. Worldwide.</td>
<td>Used U.S. and NJ rates, among others.</td>
<td>Concluded that the difference between male and female rates between fluoridated and nonfluoridated areas indicates cancer associations.</td>
<td>Concluded that the difference between male and female rates between fluoridated and nonfluoridated areas indicates cancer associations.</td>
</tr>
</tbody>
</table>

Yamouyiannis 1993

Yang et al. 2000

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for 40 cancer registries worldwide found no evidence of association with fluoride.

Cohn (1992) in New Jersey had findings suggestive of an association of fluoride in public water with increased osteosarcoma in young males. The osteosarcoma rate ratio among males below age 20 in the Cohn analysis, based on 20 cases, was 3.4 (95% confidence interval [CI] 1.8 to 6). Mahoney et al. (1991) generated bone cancer and osteosarcoma incidence rate ratios for the years 1975-1987 for fluoridated and nonfluoridated counties of New York State (excluding New York City). The authors did not observe an association of fluoridation and osteosarcoma or other bone cancers for either gender, including for those younger than age 30.

As discussed above, strengths of all the ecologic studies included the largely complete ascertainment of cases through the population-based cancer registries; the chief limitation is the potential for large amounts of bias and poor ability to adjust for covariates.

Since the 1993 NRC report, Yang et al. (2000) conducted an ecologic analysis of cancer mortality in 20 municipalities in Taiwan, half with measurable naturally occurring fluoride concentrations. They controlled for urbanization and sociodemographic variables. Bone cancers (not specifically osteosarcoma) were nonsignificantly elevated (rate ratio [RR] of 1.6, 95% CI 0.92 to 2.17) in males but decreased in females (RR of 0.87, 95% CI 0.52 to 1.44). The range of fluoride concentrations was not reported, but the median and mean were about 0.25 mg/L.

Also since 1993, four individual-based studies have been published. Gelberg (1994) and Gelberg et al. (1995) conducted a population-based case-control study of osteosarcoma before age 25 in New York State. It included 130 cases and one matched control for each case. Controls were drawn from birth certificates, with replacement for those that could not be located. Parents and/or patients were interviewed regarding residence history and exposure to fluoride through drinking water, consumer dental products, dental supplements, and fluoride treatments. Analyses were conducted according to estimated lifetime dose of fluoride in total milligrams from each source of potential exposure, both separately and combined. When data on all subjects were analyzed, total fluoride exposures showed an inverse relationship with osteosarcoma. Use of fluoride gels had strong negative associations with osteosarcoma. Based on the parents’ interviews alone (97% of subjects), the authors found negative associations with total estimated fluoride intake from all sources, particularly due to a strong negative association of osteosarcoma with estimated quantities of fluoride ingested from toothpaste. Odds ratios (ORs) were above 1.0 for all catego-

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1This study did not analyze age subgroups and, therefore, did not address particular risk for young males or females.
ries of lifetime fluoride intake from drinking water compared with those with zero estimated intake from that source, particularly among females. This distinction is particularly noteworthy because Gelberg et al. had higher estimates of the relative contributions of fluoride from toothpaste ingestion compared with drinking water than those reflected in Chapter 2 of this report (see Figure 2-1). The source of the study’s estimates of toothpaste ingestion was not specified, but the relative proportions were most similar to those shown in Figure 2-1 for ages 2 to 6. If the relative contributions from toothpaste were exaggerated, then the findings regarding fluoride specifically from drinking water could arguably be given greater weight. Analyses of average annual fluoride exposure did not differ markedly from the observations on cumulative exposure estimates, thereby controlling to some degree for age of diagnoses.

A reduced set of 59 respondent pairs who were the actual patients or their controls (i.e., excluding proxies) showed positive associations, with very wide CIs, for both fluoridated water alone and for total fluoride exposure (only combined genders were analyzed in this smaller series). There were no analyses using lagged exposure estimates to consider hypothetical latencies between potential exposures and diagnosis of osteosarcoma, so it is possible that inclusion of nonpertinent exposures could lead to misclassification of relevant exposures.

Gelberg et al. concluded that their study showed no association of osteosarcoma and fluoride exposure. To date, this study is the closest to fulfilling the recommendation of the 1993 NRC report regarding conducting one or more analytic studies of osteosarcoma and fluoride exposure. However, no bone fluoride concentrations could be assessed through this design.

Moss et al. (1995) conducted a case-control analysis of osteosarcoma in Wisconsin by using only public records (without interviews). For the 167 cases, 989 cancer controls were selected from the state cancer registry among patients with other types of cancer (brain, digestive system). The study controlled for size of town, age at diagnosis, and radium levels in drinking water and did not observe an association of fluoridation at the time of case diagnosis with osteosarcoma. Because exposure classifications were assigned without interviews or other sources of residence history or water source data, this design is similar to that of a semiecologic study. The authors also examined young age groups specifically.

A pilot hospital-based case-control study of patients under age 40 was published by McGuire et al. (1991), indicating a nonsignificant negative association with a small series of osteosarcomas (34 cases and matched controls). A full-scale case-control study by this group (Douglass 2004) is now under way. Its design is described below because of its potential for future contribution to this issue.

Grandjean et al. (1992) and Grandjean and Olsen (2004) conducted
a historical cohort study among cryolite production workers in Denmark who previously had been documented to suffer high rates of skeletal fluorosis. Cryolite is composed of about 50% fluoride, and the workers were not believed to be exposed to suspected carcinogens of any other type via their work. The authors did not control for smoking. There were no bone fluoride measurements. However, daily dose of fluoride to these workers during their time of employment could be estimated at about 30 mg/day. Over many years of employment, workers’ exposure would tend to greatly exceed chronic exposures from ingestion of fluoride at the current MCL of 4 mg/L. No osteosarcoma incident or mortality cases were observed among their 522 subjects, and, given the rarity of osteosarcoma, the authors concluded an 18-fold upper bound on the relative risks of this disease from the exposures encountered by their cohort.

The central research chapter of an unpublished dissertation by Bassin (2001) on fluoride and osteosarcoma has recently become publicly available. The author described the work as exploratory. The report has important strengths and major deficits, some of which are described below.

The design is a case-control study of people under 20 years of age from 11 teaching hospitals in the United States. Cases (n = 91) were retrospectively ascertained and 188 controls were hospitalized patients in the same orthopedics departments. Controls were matched with cases according to distance of residence from the hospital. Hospital-based controls can introduce serious selection bias; osteosarcomas treated at the participating teaching hospitals are more likely to be representative of all osteosarcomas occurring in the surrounding populations, whereas patients treated for fractures or other common orthopedic ailments at these teaching hospitals may not be as representative of the overall population that gave rise to the cases. If fluoride exposure is either a risk factor or a protective factor for the group of hospitalized controls (e.g., fracture patients), the resulting relative risk estimates could be biased downward or upward, respectively. For example, the dissertation did not provide any data on what proportion of the controls comprised fracture patients.

All subjects or their surrogates were interviewed about lifetime residence history, a strength of the design. However, individual information on key socioeconomic factors such as education and income was not collected. Average income levels based on zip codes were used but might not reflect individual socioeconomic status. Lack of such information can be problematic if socioeconomic status, or factors for which it is a surrogate, introduce confounding.

The primary exposure metrics for fluoride in drinking water were based on a combination of data from the Centers for Disease Control and Prevention, states, locales, and purveyors on year-specific water system fluoride concentrations expressed as proportions of the recommended fluoride

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guidelines. Based on tertiles for the controls, three exposure categories were expressed as 100%, 30% to 99%, and <30% of the target concentrations for fluoridated water.

A unique feature of the analysis published in the literature so far was an exploratory analysis of ORs for each specific year of age. Bassin found elevated ORs for the highest tertile compared with the lowest centering on ages 6 to 8. At age 7, the respective ORs (and 95% confidence intervals) were 7.2 (1.7 to 30.0) for males and 2.0 (0.43 to 9.28) for females. For the highest tertile, graphed results for males indicated a gradual increase and then a decrease of estimated relative risk from exposure at ages 0 to 15 with peaks at age 7, with the middle tertile, compared with the lowest, showing stable ORs across all ages. For females, both the middle and highest tertiles of exposure showed relatively unchanging relative risk estimates across exposure ages.

There was no analysis of cumulative exposures to fluoride, and therefore it is difficult to compare the Gelberg study, which used only cumulative exposure indices, with the Bassin work. This dissertation had a paucity of data in the results section, hampering its interpretation; for example, the report did not provide numbers of subjects in the categories upon which the ultimate analyses were based. Also, there were no data on bias potential stemming from nonparticipation of subjects due to refusal to be included or inability to locate them.

Nevertheless, the higher ORs for males than for females, and the highest ORs at ages 6 to 8, during what the author describes as the “mid-childhood growth spurt for boys,” are consistent with some previous ecologic or semiecolologic studies (Hoover et al. 1991; Cohn 1992) and with a hypothesis of fluoride as an osteosarcoma risk factor operating during these ages. A publication based on the Bassin thesis is expected in the spring/summer of 2006 (E. Bassin, personal communication, Jan. 5, 2006). If this paper provides adequate documentation and analyses or the findings are confirmed by another study, more weight would be given to an assessment of fluoride as a human carcinogen.

A relatively large hospital-based case-control study of osteosarcoma and fluoride exposure is under way (Douglass 2004) and is expected to be reported in the summer of 2006 (C. Douglass, Harvard School of Dental Medicine, personal communication, January 3, 2006). Most of the incident cases are identified via eight participating medical centers in California, District of Columbia, Florida, Illinois, Massachusetts, Nebraska, and Ohio. The study has prospectively identified 189 incident cases of osteosarcoma and 289 hospital controls. Controls are orthopedic patients at the same hospitals as osteosarcoma patients and include patients diagnosed with malignancies other than osteosarcoma and other patients admitted for benign tumors, injuries, and inflammatory diseases. Matching criteria include gender, age,
and geographic characteristics. The investigation includes residence histories and detailed interviews about water consumption as well as fluoride assays of bone specimens and toenails of all subjects. The ultimate analysis and validity of this study will depend partly on the degree to which control selection is not biased in such a way as to artificially increase or decrease the likelihood of fluoride exposure compared with the general population to which this study is intended to apply.

A preliminary retrospective recruitment phase of this investigation, including telephone interviews, residential history reconstruction, and an attempt to estimate dietary fluoride intakes, reported ORs of 1.2 to 1.4 that were not statistically significant (Douglass 2004). No confidence intervals were provided. The Douglass study may have limited statistical power to detect a small increase in osteosarcoma risk due to fluoride exposure, but the committee expects the forthcoming report is likely to be a useful addition to the weight of evidence regarding the presence or degree of carcinogenic hazard that fluoride ingestion might pose to osteosarcoma risk, particularly if it addresses some of the limitations of hospital-based studies that are mentioned above in the description and critique of the Bassin thesis.

**Kidney and Bladder Cancers**

The plausibility of the bladder as a target for fluoride is supported by the tendency of hydrogen fluoride to form under physiologically acid conditions, such as found in urine. Hydrogen fluoride is caustic and might increase the potential for cellular damage, including genotoxicity. The Hoover et al. (1991) analyses of the Iowa and Seattle cancer registries indicated a consistent, but not statistically significant, trend of kidney cancer incidence with duration of fluoridation. This trend has not been noted in other publications, although Yang et al. (2000) observed that the adjusted mortality rate ratios of kidney cancers among males in Taiwan was 1.55 (95% CI 0.84 to 2.84). The analogous rate for females was 1.37 (95% CI 0.51 to 3.70). Yang et al. noted statistically significant RRs in females for bladder cancer (RR = 2.79, 95% CI 1.41 to 5.55; for males RR = 1.27, 95% CI 0.75 to 2.15).

The Grandjean et al. (1992) and Grandjean and Olsen (2004) historical occupational cohort study of cryolite workers in Denmark (described earlier in the section on bone and joint cancers), who were followed from 1941 to 2002, observed an elevated standardized incidence ratio (SIR) for bladder cancers (SIR = 1.67, 95% CI 1.02 to 2.59). The SIR is the ratio of observed cases of cancer to the expected number of cases based on incidence rates of the general population. Higher SIRs were seen among males employed more than 10 years, males less than 35 years old when follow-up began, and among workers observed after a minimum latency of 30 years.
(Grandjean and Olsen 2004). In the absence of data on smoking, the authors interpreted the higher SIRs for bladder cancer than for lung cancer to suggest that smoking was unlikely to be the major cause of the elevated bladder cancer incidence. The authors proposed (2002) that excretion of fluoride compounds entailed exposure of the pertinent target tissues. As noted above, the estimated exposures of the cryolite workers were about 4-fold greater than those estimated from ingestion of fluoridated water at the MCL of 4 mg/L. However, those workers were exposed for fewer years than those involved in lifetime residency.

Romundstad et al. (2000) reported on cancer among Norwegian aluminum workers exposed to polycyclic aromatic hydrocarbons and fluorides. SIRs for bladder and lung cancer were elevated among the exposed workers. However, separate effects from the two exposures could not be distinguished from this paper. Further, the authors review and compare earlier studies that used different aluminum plant processes, which support the role of polycyclic aromatic hydrocarbons in bladder cancer among the exposed cohort. It may be noteworthy that smoking did not appear to be a confounder for the risk of bladder or lung cancer among the exposed cohort. The authors state, but do not present data, that they found a “weak association” of bladder for fluoride exposures lagged less than 20 years.

**Oral-Pharyngeal Cancer**

The NCI analysis (Hoover et al. 1991) indicated an a priori interest in oral cancers. In Iowa, one of the two cancer registries they analyzed, the authors observed a trend among males in the incidence rates of oropharyngeal cancer with duration of fluoridation, but mortality analyses did not indicate an association with fluoridation. However, in an earlier study in England, oral-pharyngeal cancers among females constituted the only site-gender category for which standardized mortality ratios in England were found to be significantly elevated in areas with naturally occurring high fluoride concentrations, defined as more than 1.0 mg/L. Twenty-four site-gender combinations were examined for 67 small areas (Chilvers and Conway 1985).

**Uterine Cancer**

An association of uterine cancer (combination of cervical and corpus uteri) with fluoridation was reported by Tohyama (1996), who observed mortality rates in Okinawa before and after fluoridation was terminated, controlling for sociodemographics. This analysis is a follow-up of the positive results from a previous exploratory analysis that comprised a large number of comparisons conducted by this researcher with the same data.
set. The only other recent publication to report on uterine cancers is that of Yang et al. (2000), who observed a mortality rate ratio of 1.25 with 95% CI of 0.98 to 1.60.

Other Specific Cancers

Respiratory cancers were elevated among the cohort of Danish cryolite miners for whom exposure was by the inhalation route (Grandjean et al. 1992; Grandejan and Olsen 2004; see discussions above on this cohort study). SIRs of 1.51 (95% CI 1.11 to 2.01) were observed for the cohort as a whole, with higher SIRs among those after 30 years of exposure and among males younger than 35 when follow-up began. No smoking data on the cohort were collected. Also, except for mortality among females in Taiwan (Yang et al. 2000), there has not been corroborating data from other analyses for respiratory cancers.

No association between lung cancer and exposure to polycyclic aromatic hydrocarbons and fluorides was found in a study of the Norwegian aluminum industry (Romundstad et al. 2000).

The NCI incidence or mortality analyses conducted by Hoover et al. (1991) observed a few suggestive increases among some subgroups for soft tissue sarcoma, non-Hodgkin's lymphoma, colorectal cancer, and lip cancer, but those cancers were not a priori of concern as related to fluoride exposure based on biologic plausibility.

All Cancers Combined

A large number of mortality analyses for all cancers combined have been reported and reviewed previously (NRC 1993; McDonagh et al. 2000a), and most of those did not detect an association of combined cancer mortality with fluoridated water. Typically, studies that only report combined cancer rates are not informative for assessing possible associations between an environmental exposure and a specific cancer outcome, particularly an uncommon cancer. Thus, the committee did not use these types of studies as part of its evaluation.

Other Studies Evaluated

The following three studies were reviewed but were not included by the committee in the evaluation of weight of evidence of carcinogenicity of fluoride for the reasons summarized below.

Takahashi et al. (2001) conducted an ecologic analysis of data from nine U.S. cities for three 5-year intervals spanning 1978-1992 combined with fluoridation data. Their analysis involved regression of log-transformed
cancer incidence rates on the log-transformed proportion of residents receiving fluoridated water. This paper is difficult to interpret and to compare with other studies in part because of its novel method of analysis. Unusual cancer subsites are included and major anatomical groupings typically appearing in cancer incidence reports (e.g., lymphocytic leukemia, breast, uterus) were omitted. Results were incompletely reported for subsets of data for particular cancer sites, creating issues of multiple comparisons and selective presentation. Another issue is that the ecologic exposure variable is the percentage of the population in each area with fluoridated water (or naturally occurring fluoride at 0.7 mg/L or higher). This is an aggregated form of a dichotomous variable on the individual level, which tends to bias results away from the null. There was inconsistent standardization of the outcome variable (which was age standardized) and the exposure variable (which was not), which can lead to bias. There was no adjustment for confounding by urbanization or other sociodemographic factors among the nine cities, which included widely different geographic, industrial, and demographic characteristics, and there was no population weighting by size. Finally, ecologic bias is best understood for linear or log-linear regression, making this study harder to interpret.

Steiner (2002) conducted an ecologic analysis of latitude, temperature, and fluoridated water in 49 cities worldwide. When fluoride concentrations were unavailable for these cities, he substituted data from neighboring areas. Average daily temperature and latitude were also included in his models, but not simultaneously. Steiner analyzed only all cancers combined. He found a negative association between cancer incidence and fluoridation.

Yiamouyiannis (1993) subtracted female from male cancer incidence rates for the United States and for New Jersey as an indication of fluoride’s carcinogenic effect among males. This paper used circular reasoning to reach a conclusion of causality; that is, it concluded that higher cancer rates in males indicate an association with fluoride on the basis of a presumed causation by fluoride of cancers in males. Because most cancers do not occur at the same rates in each gender, the committee judges it is inappropriate to subtract rates of women from those of men as a means of evaluating factors that only affect bone cancer in males.

It has been suggested that differences in osteosarcoma rates found in provinces of Kenya could be related to fluoride exposure (C. Neurath, Fluoride Action Network, unpublished data, June 17, 2005). For eight provinces of Kenya, Neurath correlated enamel fluorosis prevalences reported by Chibole (1987) with osteosarcoma incidence rates reported by Bovill et al. (1985) and found a strong association. This type of fully ecologic analysis (see Appendix C) has its inherent advantages and limitations; in this instance, however, the underlying ratios of observed-to-expected osteosarcoma incidence are not reliable because Bovill et al. do not state
that their incidence data were adjusted for differences in the age structure of various provincial populations. Bovill et al. state that Kenya is characterized by strong contrasts of ethnicity and other demographics among its geographic regions. The provincial summaries are weighted averages of the children examined, but it is not stated if they are also weighted averages of the underlying populations. Chibole does not state how the children examined in Kenyan schools and hospitals were selected (i.e., whether the fluorosis prevalence data collected were ascertained in a manner that would accurately reflect the populations of the component provinces). Chibole’s detailed table indicates a wide range of prevalences of fluorosis within many of the provinces (e.g., from 3.7% to 69.5% in the Rift Valley province).

Summary of Cancer Epidemiology Findings

The combined literature described above does not clearly indicate that fluoride either is or is not carcinogenic in humans. The typical challenges of environmental epidemiology are magnified for the evaluation of whether fluoride is a risk factor for osteosarcoma. These challenges include: detection of relatively low risks, accurate exposure classification assessment of pertinent dose to target tissues, multiple causes for the effect of interest, and multiple effects of the exposure of interest. Assessing whether fluoride constitutes a risk factor for osteosarcoma is complicated by (1) how uncommon the disease is, so that cohort or semi-ecologic studies are not based on large numbers of outcomes, and (2) the difficulty of characterizing biologic dose of interest for fluoride because of the ubiquity of population exposure to fluoride and the difficulty of acquiring bone samples in nonaffected individuals.

In summary, there has been partial but incomplete fulfillment of NRC’s recommendations on individual-based cancer studies in the intervening years since 1993; one analytic study of osteosarcoma has been published, but bone samples were not included. The alternative (hospital-based) design, including bone assays, from the Harvard group might be more useful in addressing this issue.

EPA GUIDELINES AND PRACTICE IN SETTING MCLGs REGARDING CARCINOGENICITY

The EPA Office of Drinking Water establishes MCLGs of zero for contaminants that are known or probable human carcinogens. Chemicals for which cancer hazard is judged to be absent are regulated via the reference dose (RfD) method (see Chapter 11). “Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)” reviewed EPA’s additional practice of applying an uncertainty factor between
“1 and 10” to an RfD derived from noncancer health effects (EPA 2000d). This procedure has been used for substances judged to be possibly carcinogenic in humans. That methodology document also stipulates that the water concentrations estimated to result in $10^{-6}$ to $10^{-5}$ excess cancer risks should also be assessed under the RfD scenario for comparison.

As of April 2005, EPA has adopted new “Guidelines for Carcinogen Risk Assessment,” which has replaced the 1986 categories with weight-of-evidence descriptors, involving textual consideration and explanation of how each category was arrived at. In addition, the Guidelines provide for consideration of mode of action and sensitive subpopulations, especially children (EPA 2005a,b). In addition to mode of action, other factors for weighing human epidemiologic studies and lifetime whole animal bioassays include data on biomarkers (genotoxicity and other assays of exposure, susceptibility, and effect) and toxicokinetics. Thus, key decisions about cancer pertinent to a MCLG for drinking water include an assessment of whether an MCLG of zero is appropriate based on the current epidemiologic, animal bioassay, and additional contributing data. If not, EPA will need to decide whether an uncertainty (safety) factor greater than 1.0 and up to 10.0 should be applied to an RfD derived from a precursor response to tumors.

Some recent examples of the use by EPA of RfDs with additional safety factors imposed because of possible carcinogenic hazard, based on the July 1999 Cancer Guidelines, include the MCLG for disinfection by-products (EPA 2003c). For dibromochloromethane (DBCM), EPA imposed an additional uncertainty factor of 10 to account for possible carcinogenicity based on studies of DBCM by NTP in 1985 that showed an increase in liver tumors in both genders of mice but no increase in either gender of rats. Similarly for trichloroacetic acid (TCA), an additional uncertainty factor of 10 was added to the MCLG derived from the RfD; TCA induced liver tumors in mice but not in rats. The MCLGs for all regulated chemicals considered to be possible carcinogens has included the additional 10-fold risk management factor applied to the RfD (J. Donohue, EPA, personal commun., 2004).

**FINDINGS**

The 1993 NRC report recommended the following:

Conduct one or more highly focused, carefully designed analytical studies (case control or cohort) of the cancer sites that are most highly suspect, based on data from animal studies and the few suggestions of a carcinogenic effect reported in the epidemiological literature. Such studies should be designed to gather information on individual study subjects so that adjustments can be made for the potential confounding effects of other risk factors in analyses of individu-
als. Information on fluoride exposure from sources other than water must be obtained, and estimates of exposure from drinking water should be as accurate as possible. In addition, analysis of fluoride in bone samples from patients and controls would be valuable in inferring total lifetime exposures to fluoride. Among the disease outcomes that warrant separate study are osteosarcomas and cancers of the buccal cavity, kidney, and bones and joints.

As described above, some progress in those directions have been made, with the most comprehensive study still in progress (Douglass 2004).

Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed (Tables 10-4 and 10-5). As noted above, osteosarcoma is of particular concern as a potential effect of fluoride because of (1) fluoride deposition in bone, (2) the mitogenic effect of fluoride on bone cells, (3) animal results described above, and (4) pre-1993 publication of some positive, as well as negative, epidemiologic reports on associations of fluoride exposure with osteosarcoma risk.

Several studies indicating at least some positive associations of fluoride with one or more types of cancer have been published since the 1993 NRC report. Several in vivo human studies of genotoxicity, although limited, suggest fluoride's potential to damage chromosomes. The human epidemiology study literature as a whole is still mixed and equivocal. As pointed out by Hrudey et al. (1990), rare diseases such as osteosarcoma are difficult to detect with good statistical power.

In animal studies, the overall incidence of osteosarcoma in male rats showed a positive trend. Based on the more recent historical control data (Haseman et al. 1998) that were closer to the time frame of the NTP study, the 4% to 5% incidence at the high dose might have exceeded the historical range. The relevance of rat osteosarcoma to humans was discussed based on the species differences in the development of long bone, the common site of human osteosarcoma (NTP 1990). Specifically, ossification of human long bones is completed by 18 years of age whereas it continues in rats throughout the first year of life (PHS 1991). Nevertheless, most of the osteosarcomas found in male rats were not in long bones.

In another study (NTP 1992), that used the same strain and sex of rats, no increase in osteosarcomas was reported, even though the animals were exposed to a higher concentration of fluoride than in the earlier study. However, the primary intent of the NTP (1992) study was to test the hypothesis that ionizing radiation is an initiator of osteosarcoma and that fluoride is a promoter, and the committee thought it was noteworthy that none of the irradiated animals developed osteosarcomas.

The 1993 NRC review concluded that the increase in osteoma in male and female mice (Maurer et al. 1993) was related to fluoride treatment.
### TABLE 10-4 Evidence Summary for Carcinogenicity of Fluoride: Epidemiologic Studies and Rodent Lifetime Bioassays

<table>
<thead>
<tr>
<th>Cancer Site/Type</th>
<th>Individual-Based Epidemiology Studies</th>
<th>Ecologic Epidemiology Studies</th>
<th>Animal Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>Case-control studies ambiguous (additional comprehensive hospital-based case-control study including bone fluoride measurements is under way).</td>
<td>Mixed.</td>
<td>Male F344/N rats: Borderline positive. Male F344 rats: inconclusive</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>NCI incidence elevated in males, but no mortality trends. Several other reports positive.</td>
<td></td>
<td>Nonstatistically significant increase in male rats.</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Nonstatistically significant increase in male rats.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney and/or bladder</td>
<td>Occupational cohort: positive finding, inhalation route, high exposures.</td>
<td>Some positive reports.</td>
<td></td>
</tr>
<tr>
<td>Uterine</td>
<td>One positive report.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Occupational cohort positive finding, inhalation route, high exposures.</td>
<td>One positive report.</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 10-5 Evidence Summary for Carcinogenicity of Fluoride: Genotoxicity and Mechanistic Assays

<table>
<thead>
<tr>
<th>Type of Effect and Assay</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitogenesis</td>
<td>Well established.</td>
</tr>
<tr>
<td>Cytogenetic effects: human in vivo exposure, in vitro assay.</td>
<td>Inconsistent; and the positive findings were from weak papers.</td>
</tr>
<tr>
<td>Cytogenetic effects: other mammalian systems.</td>
<td>Inconsistent.</td>
</tr>
<tr>
<td>Transformation.</td>
<td>Inconsistent; the positive results are consistent with a promotion mechanism.</td>
</tr>
<tr>
<td>DNA repair mechanism: human.</td>
<td>Suggestive positive finding regarding tumor suppressor gene, small case series.</td>
</tr>
<tr>
<td>Mutation: mammalian systems.</td>
<td>Inconsistent.</td>
</tr>
<tr>
<td>Mutation: microorganisms.</td>
<td>Negative.</td>
</tr>
</tbody>
</table>
Although the subsequent review by AFIP considered these mouse osteomas as more closely resembling hyperplasia than neoplasia, given that osteoma is widely recognized as neoplastic, the evidence of osteoma remains important in the overall weight-of-evidence consideration. The increased incidence and severity of osteosclerosis in high-dose female rats in the NTP study demonstrated the mitogenic effect of fluoride in stimulating osteoblasts and osteoid production (NTP 1990) (see also Chapter 5).

The genotoxicity data, particularly from in vivo human studies, are also conflicting; whereas three were positive on the basis of the ingestion route (Sheth et al. 1994; Wu and Wu 1995; Joseph and Gadhia 2000), all three of these reports had serious deficits in design and/or reporting, including the characterization of how the study populations were selected and whether the exposed and unexposed study subjects were comparable. Two studies (Meng et al. 1995; Meng and Zhang 1997) were positive for the inhalation route among workers in a phosphate fertilizer factory, although other contaminants cannot be ruled out as the causal factors. Contrasting negative observations by other investigators (Li et al. 1995; Jackson et al. 1997; Van Asten et al. 1998) must also be considered.

RECOMMENDATIONS

Carcinogenicity

• The results of the Douglass et al. multicenter osteosarcoma study (expected in the summer of 2006) could add important data to the current body of literature on fluoride risks for osteosarcoma because the study includes bone fluoride concentrations for cases and controls. When this study is published, it should be considered in context with the existing body of evidence to help determine what follow-up studies are needed.

• Further research on a possible effect of fluoride on bladder cancer risk should be conducted. Since bladder cancer is relatively common (compared with osteosarcoma), both cohort and case-control designs would be feasible to address this question. For example, valuable data might be yielded by analyses of cancer outcomes among the cohorts followed for other health outcomes, such as fractures (see Chapter 5).

Genotoxicity

• The positive in vivo genotoxicity studies described in the chapter were conducted in India and China, where fluoride concentrations in drinking water are often higher than those in the United States. Further, each had a dearth of information on the selection of subjects and was based on small numbers of participants. Therefore, in vivo human genotoxicity studies
in U.S. populations or other populations with nutritional and sociodemographic variables similar to those in the United States should be conducted. Documentation of subject enrollment with different fluoride concentrations would be useful for addressing the potential genotoxic hazards of fluoridated water in this country.
Drinking Water Standards for Fluoride

The U.S. Environmental Protection Agency (EPA) has three standards for fluoride in drinking water: a maximum-contaminant-level goal (MCLG), a maximum contaminant level (MCL), and a secondary maximum contaminant level (SMCL). In this chapter, the committee reviews the MCLG and SMCL for fluoride, the two nonenforceable standards, for their scientific basis and adequacy for protecting the public from adverse effects. First, an overview of current procedures for establishing exposure standards is provided, and risk assessment issues that have developed since the original MCLG and SMCL for fluoride were established are discussed.

CURRENT METHODS FOR SETTING STANDARDS FOR DRINKING WATER

To establish MCLGs for drinking water, EPA reviews studies of health effects of individual contaminants and uses the information to calculate an exposure level at which no known or anticipated adverse health effects would occur with an adequate margin of safety. MCLGs consider only public health and not the limits of detection or treatment technology, so they may be set at concentrations that water systems cannot achieve.

Noncarcinogenic Contaminants

For noncarcinogenic chemicals, the MCLG is based on the reference dose, which is defined as an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily dose to the human population
DRINKING WATER STANDARDS FOR FLUORIDE

(including susceptible subpopulations) that is likely to have no appreciable risk of deleterious health effects during a lifetime. The reference dose characterizes exposure conditions that are unlikely to cause noncancer health effects, which are typically assumed to have a threshold dose above which adverse health effects would be expected to occur.

Traditionally, reference doses are determined by identifying the most sensitive health effects that are relevant to the human, selecting a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL), and dividing the NOAEL or LOAEL by one or more uncertainty factors to provide a margin of safety. Uncertainty factors are applied to address uncertainties with using experimental animal data for human effects (interspecies differences) to account for variable susceptibilities in the human population (intraspecies differences), to adjust for differences between the LOAEL and NOAEL when a LOAEL is used instead of a NOAEL (LOAEL-to-NOAEL extrapolation), to account for uncertainties with predicting chronic exposure effects on the basis of subchronic exposure studies (subchronic to chronic extrapolation), and to address uncertainties when the database on the chemical is inadequate. Sometimes a modifying factor is used to account for additional uncertainty not addressed by the standard uncertainty factors.

Typically, uncertainty factors are assigned values ranging from 1 to 10. If information about a factor is sparse and uncertainty is high, a default value of 10 is generally used. If information is available, the uncertainty factor might be reduced to 1. For an uncertainty factor that falls between 1 and 10, a factor of 3 is typically assigned, because 3 is the approximate logarithmic mean of 1 and 10, and it is assumed that the uncertainty factor is distributed lognormally (EPA 1994). To calculate a reference dose, the NOAEL or LOAEL is divided by the product of the uncertainty factors. EPA typically uses a maximum of 3,000 for the product of four uncertainty factors that individually are greater than 1 and a maximum of 10,000 with five uncertainty factors (Dourson 1994).

More recently, the benchmark dose is being used as the starting point for calculating reference doses. The benchmark dose is a dose with a specified low level of excess health risk, generally in the range of 1% to 10%, which can be estimated from data with little or no extrapolation outside the experimental dose range. Specifically, the benchmark dose is derived by modeling the data in the observed experimental range, selecting an incidence level within or near the observed range (e.g., the effective dose producing a 10% increased incidence of response), and determining the upper confidence limit on the model. To account for experimental variation, a lower confidence limit or uncertainty factors on the benchmark dose are used to ensure that the specified excess risk is not likely to be exceeded.

To derive an MCLG, the reference dose is multiplied by a typical adult
body weight of 70 kg and divided by an assumed daily water consumption of 2 L to yield a drinking water equivalent level. That level is multiplied by a percentage of the total daily exposure contributed by drinking water (usually 20%) to calculate the MCLG. EPA then uses the MCLG to set an enforceable standard (the MCL). The MCL is set as close to the MCLG as feasible.

Carcinogenic Contaminants

EPA sets MCLGs of zero for contaminants that are known or probable human carcinogens. For chemicals judged to be possibly carcinogenic to humans, EPA has recently begun applying an uncertainty factor between 1 and 10 to the reference dose derived from noncancer health effects to determine some exposure standards, such as certain ambient water-quality criteria (EPA 2000d). EPA stipulates that the water concentrations estimated to result in $1 \times 10^{-6}$ to $1 \times 10^{-5}$ excess cancer risks should also be compared with the reference dose.

NEW RISK ASSESSMENT CONSIDERATIONS

Since the fluoride MCLG and SMCL were originally issued, there have been a number of developments in risk assessment. A few of those issues were described above in the discussion of current risk assessment practices (e.g., use of benchmark dose). Below, a few specific issues relevant to the committee’s review of the drinking water standards for fluoride are discussed, including advances in carcinogenicity assessment, relative source contribution, special considerations for children, and explicit treatment of uncertainty and variability.

Carcinogenicity Assessment

In 2005, EPA issued its new Guidelines for Carcinogen Risk Assessment (EPA 2005a) as a replacement for its 1986 guidelines (EPA 1986). The revised guidelines were issued partly to address changes in the understanding of the variety of ways in which carcinogens can operate. For example, the guidelines provide a framework that allows all relevant biological information to be incorporated and the flexibility to consider future scientific advances.

The guidelines provide several options for constructing the dose-response relationship, in contrast to the single default dose-response relationship of the 1986 cancer guidelines. Biologically based extrapolation is the preferred approach for quantifying risk. It involves extrapolating from animals to humans based on a similar underlying mode of action. However,
in the absence of data on the parameters used in such models, the guidelines allow for alternative quantitative methods. In the default approaches, response data are modeled in the range of observation and then the point of departure or the range of extrapolation below the range of observation is determined. In addition to modeling tumor data, other kinds of responses are modeled if they are considered measures of carcinogenic risk. Three default approaches—linear, nonlinear, and both—are provided. Curve fitting in the observed range provides the effective dose corresponding to the lower 95% limit on a dose associated with a low level of response (usually in the range of 1% to 10%). That dose is then used as a point of departure for extrapolating the origin as the linear default or for a margin of exposure as the nonlinear default.

Other modifications of interest in the new guidelines include the following:

- All biological information and not just tumor findings is considered in the hazard-assessment phase of risk assessment.
- Mode of action is emphasized to reduce the uncertainty in describing the likelihood of harm and in determining the dose-response approaches.
- A weight-of-evidence narrative replaces the 1986 alphanumeric classification categories. The narrative describes the key evidence, potential modes of action, conditions of hazard expression, and key default options used.
- Direction is provided on how the overall conclusion and the confidence about risk are presented and a call is made for assumptions and uncertainties to be clearly explained.

Relative Source Contribution

EPA has developed a relative source contribution policy for assessing total human exposure to a contaminant. Under this policy, nonwater sources of exposure are considered in development of the reference dose. The percentage of total exposure typically accounted for by drinking water is applied to the reference dose to determine the maximum amount of the reference dose “apportioned” to drinking water reflected by the MCLG value. In the drinking water program, the MCLG cannot account for more than 80% or for less than 20% of the reference dose (EPA 2000d). Typically, a conservative approach is used by applying a relative source contribution factor of 20% to the reference dose when exposure data are inadequate. It is assumed that the major portion (80%) of the total exposure comes from other sources, such as the diet. This policy contrasts with past “subtraction” methods of determining relative source contributions, in which
sources of exposure other than drinking water were subtracted from the reference dose.

In EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*, a process called the exposure decision tree (Figure 11-1) is proposed as another means for determining relative source

![Exposure Decision Tree](image-url)

**FIGURE 11-1** Exposure Decision Tree for Defining Proposed Reference Dose Apportionment. SOURCE: EPA 2000d. Abbreviations: POD, point of departure; UF, uncertainty factor.
contributions (EPA 2000d). This method considers the adequacy of available exposure data, levels of exposure, relevant sources/media of exposure, and regulatory agendas. The exposure decision tree approach offers flexibility in the reference dose apportionment among sources of exposure and uses chemical information (e.g., chemical and physical properties, uses of the chemical, environmental fate and transformation, likelihood of occurrence in various media) when monitoring data are inadequate. The process also allows for use of either the subtraction or the percentage method to account for other exposures, depending on whether one or more health-based criterion is relevant for the chemical in question. The subtraction method can be used when only one criterion is relevant to a chemical. In those cases, other sources of exposure can be considered “background” and can be subtracted from the reference dose (EPA 2000d).

Risk to Children

In 1996, EPA's Office of the Administrator issued Environmental Health Threats to Children (EPA 1996b) and set an agenda that called for considering children's risks in all EPA actions. Children are considered a special subpopulation because their health risks can differ from those of adults as a result of their immature physiology, metabolism, and differing levels of exposure due to factors such as greater food consumption per unit of body weight and outdoor play activities. Different levels of exposure for children are typically considered in risk assessments, but the underlying toxicity database often does not specifically address effects on children. Such limitations in toxicity data are typically addressed by applying uncertainty factors to protect susceptible populations. In 2005, EPA issued special guidance for assessing susceptibility to carcinogens during early life stages (EPA 2005b).

FLUORIDE STANDARDS

Maximum-Contaminant-Level Goal

In 1986, EPA established an MCLG for fluoride of 4 mg/L to protect against “crippling” (clinical stage III) skeletal fluorosis. At that time, a reference dose for fluoride was not available, and the MCLG was calculated from a LOAEL of 20 mg/day estimated from case studies (Moller and Gudjonsson 1932), the assumption that adult water intake is 2 L per day, and the application of a safety factor of 2.5. EPA selected the safety factor to establish an MCLG that was in agreement with a recommendation from the U.S. Surgeon General (see Chapter 1).

The committee considered three toxicity end points for which there were sufficient relevant data for assessing the adequacy of the MCLG for
fluoride to protect public health: severe enamel fluorosis, skeletal fluorosis, and bone fractures.

Severe Enamel Fluorosis

In the past, moderate to severe forms of enamel fluorosis were considered to be aesthetically displeasing but not adverse to health, largely because there was no direct evidence that moderate-to-severe enamel fluorosis, as observed in the United States, had resulted in tooth loss, loss of tooth function, or psychological problems. In reviewing the collective evidence, the committee considered moderate and severe forms of the condition separately. Severe enamel fluorosis is characterized by enamel loss and pitting. This damage compromises enamel's protective barrier and can make the teeth more susceptible to environmental stresses and to caries formation because it allows bacteria, plaque, and food particles to become entrapped in the enamel. Caries is dental decay caused by bacterial infection. When the infection goes uncheckd, cavities may form that can cause toothache and tooth sensitivity to temperature and sweets. If cavities are untreated, the infection can lead to abscess, destruction of bone, and spread of the infection to other parts of the body (USDHHS 2000). While increased risk of caries has not been firmly established, the majority of the committee found that destruction of the enamel and the clinical practice of treating the condition even in the absence of caries provide additional lines of evidence for concluding that severe enamel fluorosis is an adverse health effect. Severe enamel fluorosis occurs at an appreciable frequency, approximately 10% on average, among children in U.S. communities with water fluoride concentrations at or near the current MCLG of 4 mg/L. Thus, the committee concludes that the MCLG of 4 mg/L is not protective against severe enamel fluorosis.

Two of the 12 members of the committee did not agree that severe enamel fluorosis should now be considered an adverse health effect. They agreed that it is an adverse dental effect but found that no new evidence has emerged to suggest a link between severe enamel fluorosis, as experienced in the United States, and a person’s ability to function. They judged that demonstration of enamel defects alone from fluorosis is not sufficient to change the prevailing opinion that severe enamel fluorosis is an adverse cosmetic effect. Despite their disagreement on characterization of the condition, these two members concurred with the committee’s conclusion that the MCLG should prevent the occurrence of this unwanted condition.

Strong evidence exits that the prevalence of severe enamel fluorosis is nearly zero at water fluoride concentrations to below 2 mg/L. For example, Horowitz et al. (1972) found that partial defluorination of drinking water from 6.7 mg/L to slightly below 2 mg/L prevented severe enamel fluorosis. Moderate forms of enamel fluorosis decreased from 42% to 3%.
Skeletal Fluorosis

Skeletal fluorosis is a bone and joint condition associated with prolonged exposure to high concentrations of fluoride. Fluoride increases bone density and appears to exacerbate the growth of osteophytes in the bone and joints, which leads to the radiological characteristics of the condition and associated pain. Crippling skeletal fluorosis (or clinical stage III) is the current basis of EPA’s MCLG. The term crippling historically has been used to describe alterations in bone architecture and calcification of tissues that progress to the degree that they limit an individual’s range of motion.

The committee judges that stage II skeletal fluorosis (the stage before mobility is significantly affected) should also be considered an adverse health effect. This stage is characterized by chronic joint pain, arthritic symptoms, slightly calcified ligaments, increased osteosclerosis/cancellous bones, and possibly osteoporosis of long bones (PHS 1991). No new studies and few clinical cases of skeletal fluorosis in healthy U.S. populations have been reported in recent decades. To determine whether EPA’s MCLG protects the general public from stage II and stage III skeletal fluorosis, the committee compared pharmacokinetic predictions of bone-fluoride concentrations and historical data on iliac-crest bone-fluoride concentrations associated with the different stages of skeletal fluorosis. It found that bone-fluoride concentrations estimated to be achieved from lifetime exposure to fluoride at 4 mg/L (10,000 to 12,000 milligrams per kilogram [mg/kg] ash) fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis (4,300 to 9,200 gm/kg ash and 4,200 to 12,700 mg/kg ash, respectively). This suggests that the MCLG might not protect all individuals from the adverse stages of the condition. However, stage III skeletal fluorosis appears to be a rare condition in the United States, and the existing epidemiologic evidence is insufficient for determining whether stage II skeletal fluorosis is occurring in U.S. residents. Thus, before any conclusions can be drawn, more research is needed to clarify the relationship between fluoride ingestion, fluoride concentrations in bone, and stage of skeletal fluorosis.

Bone Fractures

The database on fluoride’s effects on bone fractures has expanded since the earlier National Research Council (NRC) review. A number of observational studies have compared bone fracture rates between populations exposed to different concentrations of fluoride in drinking water. The committee focused its review on studies involving exposure to fluoride near or within the range of 2 to 4 mg/L. Several strong studies (Sowers et al. 1991; Kurttio et al. 1999; Li et al. 2001) indicated an increased risk of bone fracture, and the results of other studies (Sowers et al. 1986; Alarcón-Herrera et
al. 2001) were qualitatively consistent with that finding. The one study using serum fluoride concentrations found no appreciable relationship to fractures (Sowers et al. 2005). Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to show an association might have been diminished.

A larger database on clinical trials of fluoride as an osteoporosis treatment was also reviewed. A meta-analysis of randomized clinical trials of fluoride reported an elevated risk of new nonvertebral fractures (1.85, 95% CI = 1.36, 2.50) and a slightly decreased risk of vertebral fractures (0.90, 95% CI = 0.71, 1.14) after 4 years (Haguenauer et al. 2000). An increased risk of bone fracture was found among those studies. Although the doses of fluoride were higher in the clinical trials than were experienced by people drinking water with fluoride at 4 mg/L, the length of exposure was shorter. Although comparison of these sets of data involves several assumptions, the ranges of estimated concentrations of bone fluoride were similar in the clinical trials (5,400 to 12,000 mg/kg ash) and observational studies (6,200 to >1,000 mg/kg ash). Pharmacokinetic modeling indicates that these concentrations of fluoride in bone could result from lifetime exposure to fluoride at 4 mg/L in drinking water.

Fracture risk and bone strength have been studied in animal models. The studies have shown that fluoride increases bone mass but results about its effect on the strength of bone are conflicting. Some investigators have reported a biphasic effect on bone strength (Beary 1969; Rich and Feist 1970; Turner et al. 1992), with lower concentrations of fluoride increasing strength and higher concentrations reducing it, but others have not found this effect (Turner et al. 1995). The weight of the evidence from laboratory studies indicates that, although fluoride might increase bone volume, strength per unit volume is lower. Studies of rats indicate that bone strength begins to decline when fluoride in bone ash reaches the range of 6,000 to 7,000 mg/kg (Turner et al. 1992). Studies in rabbits have shown that fluoride might decrease bone strength by altering the structural integrity of the bone microarchitecture (Turner et al. 1997; Chachra et al. 1999). However, more research is needed to address uncertainties associated with extrapolating animal data on bone strength and fractures to humans.

Overall, there was consensus among the committee that there is scientific evidence that under certain conditions fluoride can weaken bone and increase the risk of fractures. The majority of the committee concluded that lifetime exposure to fluoride at drinking water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure to 1 mg/L, particularly in some demographic subgroups that are prone to accumulate fluoride in their bones (e.g., people with renal disease). However, 3 of the 12 members judged that the evidence only supported a conclusion that the MCLG might not be protective against bone fracture.
These members judge that more evidence is needed that bone fractures occur at an appreciable frequency in human populations exposed to fluoride at 4 mg/L before drawing a conclusion that the MCLG is likely to be not protective.

Secondary Maximum Contaminant Level

EPA established an SMCL of 2 mg/L on the basis of cosmetically “objectionable” enamel fluorosis, defined as discoloration and/or pitting of teeth. The SMCL was selected to prevent objectionable enamel fluorosis in a significant portion of the population. EPA reviewed data on the prevalence of moderate and severe enamel fluorosis and found that, at a fluoride concentration of 2 mg/L in drinking water, the prevalence of moderate fluorosis ranged from 4% to 15% and that severe cases were observed at concentrations above 2.5 mg/L. Because of the anticaries properties of fluoride, EPA judged 2 mg/L to be an adequate upper-boundary guideline to limit the occurrence of objectionable enamel fluorosis and provide some anticaries benefit. The SMCL is not a recommendation to add fluoride to drinking water. The SMCL is a guideline for naturally occurring fluoride to be used by the states for reducing the occurrence and severity of enamel fluorosis, a condition considered by EPA to be a cosmetic condition. If fluoride in a community water system exceeds the SMCL but not the regulatory MCL, a notice about the potential risk of enamel fluorosis must be sent to all customers served by the system. The committee evaluated the SMCL only in terms of its protection against adverse cosmetic and health effects, including enamel fluorosis, skeletal fluorosis, and bone fracture. Prevention of caries was not evaluated.

Enamel Fluorosis

The committee considers moderate enamel fluorosis to be a cosmetic effect, because the available data are inadequate for categorizing the moderate form as adverse to health on the basis of structural or psychological effects. There are no studies since 1993 to assess the prevalence of enamel fluorosis at 2 mg/L, but previous reports have shown a distinct increase (approximately 15%) in moderate enamel fluorosis around 2 mg/L. Thus, the SMCL will not completely prevent the occurrence of moderate enamel fluorosis. As noted above, SMCL was intended to reduce the severity and occurrence of the condition to 15% or less of the exposed population. The available data indicates that less than 15% of children would experience moderate enamel fluorosis of aesthetic concern (discoloration of the front teeth). However, the degree to which moderate enamel fluorosis might go
beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is not known.

While a few cases of severe enamel fluorosis occasionally have been reported in populations exposed at 2 mg/L, it appears that other sources of exposure to fluoride or other factors contributed to the condition. For example, similar rates of severe enamel fluorosis were reported in populations exposed to negligible amounts of fluoride in drinking water and in populations exposed at 2 mg/L (Selwitz et al. 1995; Kumar and Swango 1999; Nowjack-Raymer et al. 1995). Thus, the committee concludes that the SMCL of 2 mg/L adequately protects the public from the most severe stage of the condition (enamel pitting).

Skeletal Fluorosis

Few new data are available on skeletal fluorosis in populations exposed to fluoride in drinking water at 2 mg/L. Thus, the committee’s evaluation was based on new estimates of the accumulation of fluoride into bone (iliac crest/pelvis) at that concentration (on average 4,000 to 5,000 mg/kg ash) and historical information on stage II skeletal fluorosis (4,300 to 9,200 mg/kg ash). A comparison of the bone concentrations indicates that lifetime exposure at the SMCL could lead to bone fluoride concentrations that historically have been associated with stage II skeletal fluorosis. However, as noted above, the existing epidemiologic evidence is insufficient for determining whether stage II skeletal fluorosis is occurring in U.S. residents, so no quantitative conclusions could be made about risks or safety at 2-mg/L exposures.

Bone Fracture

There were few studies to assess bone fracture risk in populations exposed to fluoride at 2 mg/L in drinking water. The best available study was from Finland, which provided data that suggested an increased rate of hip fracture in populations exposed to fluoride at >1.5 mg/L (Kurttio et al. 1999). However, this study alone is not sufficient to base judgment of fracture risk for people exposed to fluoride at 2 mg/L in drinking water. Thus, no quantitative conclusions could be drawn about fracture risk or safety at the SMCL.

Susceptible Subpopulations

Populations in need of special consideration when determining the MCLG and SMCL for fluoride include those at risk because their exposure to fluoride is greater than that of the average person or because they are
particularly vulnerable to the effects of fluoride. The first category includes people who consume much larger volumes of water than assumed by EPA, such as athletes and outdoor workers, who consume large volumes of water to replace fluids lost because of strenuous activity, and people with medical conditions that cause them to consume excessive amounts of water (e.g., diabetes insipidus). Individuals who consume well over 2 L of water per day will accumulate more fluoride and reach critical bone concentrations before the average water drinker exposed to the same concentration of fluoride in drinking water. In Chapter 2, it was estimated that for high-water-intake individuals, drinking water would contribute 92% to 98% of the exposure to fluoride at 4 mg/L and 86% to 96% at 2 mg/L. Another consideration is individuals who are exposed to other significant sources of fluoride, such as occupational, industrial, and therapeutic sources.

There are also environmental, metabolic, and disease conditions that cause more fluoride to be retained in the body. For example, fluoride retention might be affected by environments or conditions that chronically affect urinary pH, including diet, drugs, altitude, and certain diseases (e.g., chronic obstructive pulmonary disease) (reviewed by Whitford 1996). It is also affected by renal function, because renal excretion is the primary route of fluoride elimination. Age and health status can affect renal excretion. Individuals with renal disease are of particular concern because their ability to excrete fluoride can be seriously inhibited, causing greater uptake of fluoride into their bones. However, the available data are insufficient to provide quantitative estimates of the differences between healthy individuals and people with renal disease.

Another category of individuals in need of special consideration includes those who are particularly susceptible or vulnerable to the effects of fluoride. For example, children are vulnerable for developing enamel fluorosis, because the condition occurs only when there is exposure while teeth are being formed (the pre-eruption stages). Thus, children up to the age of 8 are the susceptible subpopulation of concern for that end point. The elderly are another population of concern because of their long-term accumulation of fluoride into their bones. There are also medical conditions that can make people more susceptible to the effects of fluoride.

Relative Source Contribution

At the time the MCLG was established for fluoride, a reference dose was not available and the MCLG was calculated directly from available data rather than as an apportioned part of the reference dose. In Chapter 2, the committee shows that at 4 mg/L, drinking water is the primary contributor to total fluoride exposure, ranging from 72% to 94% for average-water-intake individuals and from 92% to 98% for high-water-intake individuals.
At 2 mg/L, drinking water contributes 57% to 90% for average-water-intake individuals and 86% to 96% for high-water-intake individuals. Thus, it is important that future revisions to the MCLG take into consideration that water is a significant, and sometimes the most significant, source of exposure to fluoride.

**FINDINGS AND RECOMMENDATIONS**

**Maximum-Contaminant-Level Goal**

In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that EPA's MCLG of 4 mg/L should be lowered. Lowering the MCLG will prevent children from developing severe enamel fluorosis and will reduce the lifetime accumulation of fluoride into bone that the majority of the committee concluded is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis, which are particular concerns for subpopulations that are prone to accumulating fluoride in their bone.

Recommendation: To develop an MCLG that is protective of severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures, EPA should update the risk assessment of fluoride to include new data on health risks and better estimates of total exposure (relative source contribution) in individuals and to use current approaches to quantifying risk, considering susceptible subpopulations, and characterizing uncertainties and variability.

**Secondary Maximum Contaminant Level**

The prevalence of severe enamel fluorosis is very low (near zero) at fluoride concentrations below 2 mg/L. However, from a cosmetic standpoint, the SMCL does not completely prevent the occurrence of moderate enamel fluorosis. EPA has indicated that the SMCL was intended to reduce the severity and occurrence of the condition to 15% or less of the exposed population. The available data indicates that fewer than 15% of children would experience moderate enamel fluorosis of aesthetic concern (discoloration of the front teeth). However, the degree to which moderate enamel fluorosis might go beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is not known.

Recommendations: Additional studies, including longitudinal studies, of the prevalence and severity of enamel fluorosis should be done in U.S. communities with fluoride concentrations greater than
1 mg/L. These studies should focus on moderate and severe enamel fluorosis in relation to caries and in relation to psychological, behavioral, and social effects among affected children, among their parents, and among affected children after they become adults.

To better define the aesthetics of enamel fluorosis, methods should be developed and validated to objectively assess enamel fluorosis. Staining and mottling of the anterior teeth should be distinguished from staining of the posterior teeth so that aesthetic consequences can be more easily assessed.
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APPENDIX

A

Biographical Information on the Committee on Fluoride in Drinking Water

JOHN DOULL (Chair) is professor emeritus of pharmacology and toxicology at the University of Kansas Medical School. His distinguished career in toxicology includes service in a variety of leadership positions and on numerous scientific advisory committees. Most notably, he is past president of the Society of Toxicology and the American Board of Toxicology. Dr. Doull is the recipient of many awards, including the International Achievement Award from the International Society for Regulatory Toxicology and Pharmacology, the Commanders Award for Public Service from the Department of the Army, and the Stockinger Award from the American Conference of Governmental Industrial Hygienists. He was the first recipient of the John Doull Award, which was established by the Central States Chapter of the Society of Toxicology to recognize his contributions to the discipline of toxicology. He is former chair of the NRC Committee on Toxicology and former vice chair of the Board on Environmental Studies and Toxicology. He is a national associate of the National Academies. Dr. Doull received his M.D. and Ph.D. in pharmacology from the University of Chicago.

KIM BOEKELHEIDE is professor and acting chair of the Department of Pathology and Laboratory Medicine at Brown University. His research interests are in male reproductive biology and toxicology, particularly the potential roles of germ-cell proliferation and apoptosis and local paracrine growth factors in regulating spermatogenesis after toxicant-induced injury. Dr. Boekelheide serves on the NRC Committee on Toxicity Testing and Assessment of Environmental Agents and has served on the Committee on Gender Differences in Susceptibility to Environmental Factors: A Priority
Assessment. He is a past member of the Board of Scientific Counselors of the National Toxicology Program (NTP), currently serves on the NTP Center for the Evaluation of Risks to Human Reproduction expert panel that is evaluating di-(2-ethylhexyl)phthalate, and was chair of the National Institutes of Health Center for Scientific Review Special Emphasis Panel, Fetal Basis of Adult Disease: Role of the Environment. Dr. Boekelheide received his M.D. and Ph.D. in pathology from Duke University and is board certified in anatomic and clinical pathology.

BARBARA FARISHIAN is a practicing dentist in Washington, DC, and is on the faculty of the University of Maryland Dental School. She is a fellow of the Academy of General Dentistry, past president of the Capitol Academy of Dentistry, and a member of the Board of Directors of the District of Columbia Dental Society, an affiliate of the American Dental Association. Before attending dental school, Dr. Farishian was a toxicologist at the U.S. Environmental Protection Agency and was on the biomedical research staff of the Wistar Institute of the University of Pennsylvania. She received her D.D.S. from the Georgetown University Dental School.

ROBERT L. ISAACSON is a distinguished professor of psychology at Binghamton University. His research interests are in behavioral neuroscience, particularly the study of recovery from brain damage, functions of the limbic system, mechanisms responsible for neuronal cell death, and the neurotoxic effects of certain fluoride complexes. He is a past president of the International Behavioral Neuroscience Society and is a recipient of the Society’s Lifetime Achievement Award. He serves on a number of editorial boards, including that of Brain Research. He has received fellow status in several scientific societies. He has served as chairperson and member of several committees of the Society for Neuroscience. In the past he has served as a member of grant review panels for the National Institutes of Health, the National Institute of Mental Health, and the National Science Foundation. He received his Ph.D. from the University of Michigan.

JUDITH B. KLOTZ is an adjunct associate professor at the University of Medicine and Dentistry of New Jersey School of Public Health. Previously, she was program manager of the cancer surveillance and environmental epidemiology programs at the New Jersey Department of Health and Senior Services. Her research interests are in epidemiological studies of cancer incidence and reproductive outcomes, gene-environment interactions, evaluation of biological exposures to environmental contaminants, and the application of health risk assessment and epidemiology to public policy. She received her M.S. in genetics from the University of Michigan and her
Dr. P.H. in environmental health sciences from Columbia University School of Public Health.

JAYANTH V. KUMAR is director of the Oral Health Surveillance & Research Unit, Bureau of Dental Health, at the New York State Department of Health. He also holds an appointment as an associate professor in the Department of Health Policy, Management, and Behavior at the School of Public Health of the University at Albany, State University of New York. He is a diplomate and former president of the American Board of Dental Public Health. His research interests are in exposure to fluoride, its effects on oral health, and health promotion and disease prevention strategies. Dr. Kumar received his dental degree from Bangalore University, M.P.H. from Johns Hopkins University, and postdoctoral certificate in dental public health from the New York State Department of Health.

HARDY LIMEBACK is an associate professor and head of preventive dentistry at the University of Toronto; he is also a part-time practicing dentist. His research interests are in tooth development, enamel proteins, caries, and prevention of dental fluorosis. Dr. Limeback is a former president of the Canadian Association of Dental Research. He has been involved for many years in reviewing the scientific literature related to fluoridation of drinking water. He received his Ph.D. in collagen biochemistry and his D.D.S. from the University of Toronto.

CHARLES POOLE is an associate professor in the Department of Epidemiology at the University of North Carolina School of Public Health. Previously, he was with the Boston University School of Public Health. Dr. Poole’s work currently focuses on the development and utilization of epidemiologic methods and principles, including problem definition, study design, data collection, statistical analysis, and interpretation and application of research results, including systematic review and meta-analysis. His research experience includes studies in environmental and occupational epidemiology and other substantive areas. Dr. Poole was an epidemiologist in the Office of Pesticides and Toxic Substances of the U.S. Environmental Protection Agency for 5 years and worked for a decade as an epidemiologic consultant, both with a firm and independently. He received his M.P.H in health administration from the University of North Carolina School of Public Health and his Sc.D. in epidemiology from the Harvard School of Public Health. Dr. Poole was a member of the Institute of Medicine Committee on Gulf War and Health: Review of the Literature on Pesticides and Solvents and the National Research Council Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations.
J. EDWARD PUZAS is the Donald and Mary Clark Professor of Orthopedics at the University of Rochester School of Medicine and Dentistry. He also holds faculty appointments in biochemistry, biomedical engineering, oncology, and pathology and laboratory medicine. He is director of the university’s Osteoporosis Center and Center for Musculoskeletal Research. His research interests are in all aspects of bone, cartilage, orthopaedic, and dental biology, with a particular interest in diseases of the skeleton, such as osteoporosis and some skeletal cancers. He also directs the osteotoxicology research core at the university’s National Institutes of Environmental Health Sciences center program at the University of Rochester Medical Center, where he conducts research on adverse impacts of environmental agents on skeletal tissue. He has won several awards for his research, including the Kappa Delta Prize for Outstanding Orthopaedic Research and the Kroc Foundation Award for Excellence in Cartilage and Bone Research. Dr. Puzas is president of the Orthopaedic Research Society. He received his M.S. and Ph.D. in radiation biology and biophysics from the University of Rochester.

NU-MAY RUBY REED is a staff toxicologist with the California Environmental Protection Agency’s (Cal/EPA) Department of Pesticide Regulation, where she is the lead person on risk assessment issues in the health assessment section. Her research interests are in evaluating health risks and developing dietary assessment guidelines for pesticides. She has been on several Cal/EPA working groups that initiate, research, and revise risk assessment guidelines and policies, and she represented her department in task forces on community concerns and emergency response, risk management guidance, and public education. Dr. Reed is also a lecturer on health risk assessment at the University of California at Davis. She received her Ph.D. from the University of California at Davis and is a diplomate of the American Board of Toxicology.

KATHLEEN M. THIESEN is a senior scientist at SENES Oak Ridge, Inc., Center for Risk Analysis. She has extensive experience in evaluating exposures, doses, and risks to human health from environmental contaminants and in using uncertainty analysis for environmental and health risk assessment. More recently, Dr. Thiessen has led a working group on dose reconstruction for the International Atomic Energy Agency’s Biosphere Modeling and Assessment Methods program. She received her Ph.D. in genetics from the University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences.

THOMAS WEBSTER is assistant professor in the Department of Environmental Health at the Boston University School of Public Health. His
research interests include methods in environmental epidemiology (particularly spatial epidemiology and ecologic bias), applications of mathematical modeling to toxicology and epidemiology, and persistent organic pollutants, particularly brominated fire retardants. He received his D.Sc. in environmental health from the Boston University School of Public Health.
APPENDIX

B

Measures of Exposure to Fluoride in the United States: Supplementary Information

U.S. DATA ON ARTIFICIAL AND NATURAL FLUORIDE IN DRINKING WATER

The recommended “optimal” fluoride concentrations for community public water supply systems and school public water supply systems are shown in Table B-1. Both sets of recommendations are based on the “annual average of maximum daily air temperatures” (CDC 1995, based on two studies in the 1950s). Table B-2 provides the approximate number of persons receiving artificially fluoridated public water in 1992, by fluoride concentration. In practice, most states seem to use a single fluoride concentration for the whole state. Figure B-1 shows the fluoride concentration by state with respect to annual average temperature for that state over the period 1971-2000. Table B-3 presents the approximate number of persons receiving naturally fluoridated public water in 1992, by fluoride concentration.

The number of persons served with public water supplies exceeding 4 milligrams (mg) of fluoride per liter (L) is expected to be substantially lower now than in 1992. For example, South Carolina, which had more than half of the persons in that category in 1992 (Table B-3), now has only occasional violations of the maximum contaminant level (MCL) (e.g., two water systems with 10 violations in calendar year 2003; SCDHEC 2004). On the other hand, a recent news article indicates that some areas in Virginia

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1See also local drinking water information by state at http://www.epa.gov/safewater/dwinfo.htm.
### TABLE B-1 Recommended Optimal Fluoride Concentrations for Public Water Supply Systems

<table>
<thead>
<tr>
<th>Annual Average of Maximum Daily Air Temperatures&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recommended Fluoride Concentrations, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>°F</td>
<td>°C</td>
</tr>
<tr>
<td>50.0-53.7</td>
<td>10.0-12.0</td>
</tr>
<tr>
<td>53.8-58.3</td>
<td>12.1-14.6</td>
</tr>
<tr>
<td>58.4-63.8</td>
<td>14.7-17.7</td>
</tr>
<tr>
<td>63.9-70.6</td>
<td>17.8-21.4</td>
</tr>
<tr>
<td>70.7-79.2</td>
<td>21.5-26.2</td>
</tr>
<tr>
<td>79.3-90.5</td>
<td>26.3-32.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on temperature data obtained for a minimum of 5 years.

<sup>b</sup>Based on 4.5 times the optimal fluoride level for communities. School water fluoridation is recommended only when the school has its own source of water and is not connected to a community water system. Several other criteria are also considered; for example, if >25% of the children attending the school already receive optimally fluoridated water at home, the school’s water should not be fluoridated.

**SOURCE:** CDC 1995.

are still served by water systems with fluoride exceeding 4 mg/L (Hirschauer 2004).

Miller-Ihli et al. (2003) reported on fluoride concentrations in water samples collected in 1999 from 24 locations nationwide; these locations were expected to provide nationally representative samples for the National Food and Nutrient Analysis Program. Not unexpectedly, their findings indicate a bimodal distribution of fluoride concentrations in public drinking water: either water was fluoridated at approximately 1 mg/L or it was not fluoridated, with concentrations bordering on undetectable.

### WATER INGESTION AND FLUORIDE INTAKES

Tables B-4 to B-7 summarize recent estimates by the U.S. Environmental Protection Agency (EPA) of the mean and selected percentiles of water ingestion by source (community supplies, bottled water, “other” sources, and all sources combined) and subpopulation (EPA 2000a); Tables B-8 and B-9

<sup>2</sup>Miller-Ihli et al. (2003) reported that 40% of the samples were fluoridated and suggested that, rather than using an average fluoride concentration for the country, an individual should be assumed to have a 40% probability of ingesting fluoridated water and a 60% probability of ingesting nonfluoridated water. However, CDC (2002a) estimates that about two-thirds of the U.S. population served by public water supplies receives fluoridated water. Thus, the sampling reported by Miller-Ihli et al. was probably not sufficiently representative on a population-weighted basis.
give the corresponding estimates for consumption of community water or all water as a function of body weight. The data in Tables B-4 through B-9 are for those persons who actually consume water from the indicated source, rather than per capita estimates for the entire population. Estimates include plain (noncarbonated) drinking water and indirect water (water added to foods and beverages during preparation at home or by local food service establishments). Water in processed foods (commercial water) or naturally contained in foods (biological water) was not included.
FIGURE B-1 Level of artificial fluoridation in 1992 by state (Table B-2; CDC 1993) versus area-weighted annual average temperature (°F) for that state over the period 1971-2000 (NCDC 2002a). Temperature for the District of Columbia is for Climate District 4 of the state of Maryland (NCDC 2002b). States with a range of artificial fluoride levels (Arizona, Colorado, Delaware, Iowa, Montana, New Hampshire, Texas, and Wyoming) are included at each relevant fluoride level. Arkansas and Puerto Rico are not included because of the lack of information on fluoride levels. Thin line indicates the “recommended optimal fluoride levels” for the given range of “annual average of maximum daily air temperatures” (emphasis added; Table B-1; CDC 1995).

EPA’s estimates are based on U.S. Department of Agriculture surveys taken in 1994, 1995, and 1996 of food ingestion data for two nonconsecutive days for a sample of more than 15,000 individuals in the 50 states and the District of Columbia selected to represent the entire U.S. population based on 1990 census data (EPA 2000a). (An additional survey of children in 1998 was included in the estimates used in Chapter 2.) Because these estimates were developed for the purpose of estimating people’s exposures to substances in drinking water and also are based on relatively recent data,
### TABLE B-3 Population Sizes by Level of Natural Fluoridation in 1992

<table>
<thead>
<tr>
<th>State</th>
<th>Reported Range, mg/L</th>
<th>Reported Level of Natural Fluoride, mg/L</th>
<th>Not given(^b)</th>
<th>Reported Total(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤1.2</td>
<td>1.3-1.9</td>
<td>2.0-3.9</td>
</tr>
<tr>
<td>Alabama</td>
<td>0.7-3.6</td>
<td>27,368</td>
<td>25,195</td>
<td>6,827</td>
</tr>
<tr>
<td>Arizona</td>
<td>0.7-7.4</td>
<td>242,309</td>
<td>63,132</td>
<td>39,259</td>
</tr>
<tr>
<td>Arkansas</td>
<td>NA(^d)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>California</td>
<td>0.7-3.5</td>
<td>389,715</td>
<td>24,583</td>
<td>500</td>
</tr>
<tr>
<td>Colorado</td>
<td>0.1-11.2</td>
<td>363,905</td>
<td>75,755</td>
<td>361,969</td>
</tr>
<tr>
<td>Connecticut</td>
<td>0.7-1.9</td>
<td>870</td>
<td>160</td>
<td>0</td>
</tr>
<tr>
<td>Delaware</td>
<td>0.6-0.9</td>
<td>7,171</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Florida</td>
<td>0.5-3.6</td>
<td>890,443</td>
<td>37,435</td>
<td>1,227</td>
</tr>
<tr>
<td>Georgia</td>
<td>0.7-2.0</td>
<td>16,039</td>
<td>878</td>
<td>1,200</td>
</tr>
<tr>
<td>Hawaii</td>
<td>0.7</td>
<td>354</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Idaho</td>
<td>0.6-15.9</td>
<td>293,127</td>
<td>8,275</td>
<td>2,650</td>
</tr>
<tr>
<td>Illinois</td>
<td>0.7-4.0</td>
<td>291,600</td>
<td>91,237</td>
<td>56,481</td>
</tr>
<tr>
<td>Indiana</td>
<td>0.7-4.4</td>
<td>177,890</td>
<td>36,254</td>
<td>5,541</td>
</tr>
<tr>
<td>Iowa</td>
<td>0.7-7.0</td>
<td>186,936</td>
<td>90,182</td>
<td>28,848</td>
</tr>
<tr>
<td>Kansas</td>
<td>0.5-2.6</td>
<td>81,884</td>
<td>14,958</td>
<td>22,846</td>
</tr>
<tr>
<td>Kentucky</td>
<td>NA(^e)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Louisiana</td>
<td>0.7-3.8</td>
<td>302,520</td>
<td>44,787</td>
<td>12,599</td>
</tr>
<tr>
<td>Maryland</td>
<td>0.3-5.1</td>
<td>36,583</td>
<td>11,705</td>
<td>100</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>1.0-1.1</td>
<td>122</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Michigan</td>
<td>0.7-1.9</td>
<td>114,605</td>
<td>9,968</td>
<td>0</td>
</tr>
<tr>
<td>Minnesota</td>
<td>0.7-3.2</td>
<td>2,386</td>
<td>908</td>
<td>367</td>
</tr>
<tr>
<td>Mississippi</td>
<td>0.8-3.5</td>
<td>93,120</td>
<td>9,965</td>
<td>1,560</td>
</tr>
<tr>
<td>Missouri</td>
<td>0.7-5.0</td>
<td>74,412</td>
<td>58,168</td>
<td>16,906</td>
</tr>
<tr>
<td>Montana</td>
<td>0.1-7.3</td>
<td>85,452</td>
<td>3,923</td>
<td>7,171</td>
</tr>
<tr>
<td>Nebraska</td>
<td>0.3-1.4</td>
<td>31,246</td>
<td>4,352</td>
<td>0</td>
</tr>
<tr>
<td>Nevada</td>
<td>0.5-2.6</td>
<td>16,440</td>
<td>3,628</td>
<td>5,187</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>1.0-3.9</td>
<td>12,612</td>
<td>3,749</td>
<td>11,190</td>
</tr>
</tbody>
</table>

### Notes:
- \(^a\) Alaska, the District of Columbia, Maine, Pennsylvania, Rhode Island, Tennessee, and Vermont reported no water systems with natural fluoridation.
- \(^b\) Reported as 0.0 or some other number suspected to be a misprint.
- \(^c\) Total given in the summary table for each state. Because of apparent internal inconsistencies, the numbers in the preceding columns do not necessarily give the same total.
- \(^d\) Data for Arkansas were not provided (the table for Arkansas contained a duplication of the Alaska data).
- \(^e\) Reported as 0.0 for all systems with natural fluoride.

**SOURCE:** CDC 1993.

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Fluoride in Drinking Water: A Scientific Review of EPA's Standards 

http://www.nap.edu/catalog/11571.html
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<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 1.2</td>
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<tr>
<td></td>
<td></td>
<td>≥ 4.0</td>
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<td>58,556 4,295 261</td>
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<td>0</td>
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<td>325 0</td>
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<td>5,205</td>
<td>6,002</td>
<td>6,024 3,793</td>
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<tr>
<td>Ohio</td>
<td>0.8-2.8</td>
<td>131,963</td>
<td>104,558</td>
<td>13,450 0</td>
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<tr>
<td>Oklahoma</td>
<td>0.7-12.0</td>
<td>62,353</td>
<td>20,803</td>
<td>8,966 18,895</td>
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<tr>
<td>Oregon</td>
<td>0.7-2.4</td>
<td>39,865</td>
<td>2,320</td>
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<tr>
<td>South Carolina</td>
<td>0.1-5.9</td>
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<td>27,968</td>
<td>190,430 105,618</td>
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<tr>
<td>South Dakota</td>
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<td>10,097</td>
<td>14,053</td>
<td>41,038 692</td>
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<td>Texas</td>
<td>0.7-8.8</td>
<td>2,234,504</td>
<td>426,341</td>
<td>233,326 36,863 25,200</td>
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<tr>
<td>Utah</td>
<td>0.7-2.0</td>
<td>8,240</td>
<td>2,560</td>
<td>0</td>
</tr>
<tr>
<td>Virginia</td>
<td>0.7-6.3</td>
<td>8,418</td>
<td>11,423</td>
<td>207,924 18,726 408</td>
</tr>
<tr>
<td>Washington</td>
<td>0.7-2.7</td>
<td>54,460</td>
<td>3,117</td>
<td>4,916 0</td>
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<tr>
<td>West Virginia</td>
<td>1.2</td>
<td>659</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>0.7-2.7</td>
<td>90,713</td>
<td>36,570</td>
<td>50,140 0</td>
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<tr>
<td>Wyoming</td>
<td>0.7-4.5</td>
<td>14,694</td>
<td>21,984</td>
<td>2,144 120</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>6,674,302</td>
<td>1,406,165</td>
<td>1,424,634</td>
<td>201,898 301,501</td>
</tr>
</tbody>
</table>

*a* Alaska, the District of Columbia, Maine, Pennsylvania, Rhode Island, Tennessee, and Vermont reported no water systems with natural fluoridation.

*b* Reported as 0.0 or some other number suspected to be a misprint.

*c* Total given in the summary table for each state. Because of apparent internal inconsistencies, the numbers in the preceding columns do not necessarily give the same total.

*d* Data for Arkansas were not provided (the table for Arkansas contained a duplication of the Alaska data).

*e* Reported as 0.0 for all systems with natural fluoride.

**SOURCE:** CDC 1993.
**TABLE B-4** Estimated Average Daily Water Ingestion (mL/day) from Community Sources During 1994-1996, by People Who Consume Water from Community Sources

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>1,000</td>
<td>785</td>
<td>2,069</td>
<td>2,600</td>
<td>4,273</td>
<td>14,012</td>
<td>242,641,675</td>
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<td>&lt;0.5 year</td>
<td>529</td>
<td>543</td>
<td>943</td>
<td>1,064</td>
<td>1,366</td>
<td>111</td>
<td>1,062,136</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>502</td>
<td>465</td>
<td>950</td>
<td>1,122</td>
<td>1,529</td>
<td>135</td>
<td>1,449,698</td>
</tr>
<tr>
<td>1-3 years</td>
<td>351</td>
<td>267</td>
<td>719</td>
<td>952</td>
<td>1,387</td>
<td>1,625</td>
<td>10,934,001</td>
</tr>
<tr>
<td>4-6 years</td>
<td>454</td>
<td>363</td>
<td>940</td>
<td>1,213</td>
<td>1,985</td>
<td>1,110</td>
<td>11,586,320</td>
</tr>
<tr>
<td>7-10 years</td>
<td>485</td>
<td>377</td>
<td>995</td>
<td>1,241</td>
<td>1,999</td>
<td>884</td>
<td>14,347,058</td>
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<tr>
<td>11-14 years</td>
<td>641</td>
<td>473</td>
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<td>1,742</td>
<td>2,564</td>
<td>759</td>
<td>14,437,898</td>
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<tr>
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<td>2,159</td>
<td>3,863</td>
<td>777</td>
<td>16,735,467</td>
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<tr>
<td>20-24 years</td>
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<td>711</td>
<td>2,175</td>
<td>3,082</td>
<td>5,356</td>
<td>644</td>
<td>17,658,027</td>
</tr>
<tr>
<td>25-54 years</td>
<td>1,171</td>
<td>965</td>
<td>2,326</td>
<td>2,926</td>
<td>4,735</td>
<td>4,599</td>
<td>106,779,569</td>
</tr>
<tr>
<td>55-64 years</td>
<td>1,242</td>
<td>1,111</td>
<td>2,297</td>
<td>2,721</td>
<td>4,222</td>
<td>1,410</td>
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<tr>
<td>≥ 65 years</td>
<td>1,242</td>
<td>1,149</td>
<td>2,190</td>
<td>2,604</td>
<td>3,668</td>
<td>1,958</td>
<td>28,167,077</td>
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<tr>
<td>Males (all)</td>
<td>1,052</td>
<td>814</td>
<td>2,164</td>
<td>2,733</td>
<td>4,616</td>
<td>7,082</td>
<td>118,665,763</td>
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<tr>
<td>&lt;1 year</td>
<td>462</td>
<td>441</td>
<td>881</td>
<td>1,121</td>
<td>1,281</td>
<td>118</td>
<td>1,191,526</td>
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<tr>
<td>1-10 years</td>
<td>444</td>
<td>355</td>
<td>934</td>
<td>1,155</td>
<td>1,731</td>
<td>1,812</td>
<td>18,847,070</td>
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<tr>
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<td>3,984</td>
<td>768</td>
<td>15,923,625</td>
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<tr>
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<td>1,038</td>
<td>2,387</td>
<td>3,016</td>
<td>4,939</td>
<td>4,384</td>
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<td>Females (all)</td>
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<td>2,482</td>
<td>3,863</td>
<td>6,930</td>
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<tr>
<td>&lt;1 year</td>
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<td>542</td>
<td>967</td>
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<td>1,584</td>
<td>128</td>
<td>1,320,308</td>
</tr>
<tr>
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<td>329</td>
<td>940</td>
<td>1,109</td>
<td>2,014</td>
<td>1,807</td>
<td>18,020,621</td>
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<tr>
<td>11-19 years</td>
<td>638</td>
<td>457</td>
<td>1,382</td>
<td>1,774</td>
<td>2,598</td>
<td>768</td>
<td>15,249,740</td>
</tr>
<tr>
<td>≥ 20 years</td>
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<td>943</td>
<td>2,165</td>
<td>2,711</td>
<td>4,268</td>
<td>4,227</td>
<td>89,385,243</td>
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<td>1,665</td>
<td>1,646</td>
<td>2,959</td>
<td>3,588</td>
<td>4,098</td>
<td>34</td>
<td>971,057</td>
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<tr>
<td>Pregnant women</td>
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<td>553</td>
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<td>2,388</td>
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<td>65</td>
<td>1,645,365</td>
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<tr>
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<td>756</td>
<td>2,044</td>
<td>2,722</td>
<td>4,397</td>
<td>2,176</td>
<td>55,251,477</td>
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</table>

**SOURCE:** EPA 2000a.
<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
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<td>1,967</td>
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<td>896</td>
<td>951</td>
<td>1,193</td>
<td>51</td>
<td>538,267</td>
</tr>
<tr>
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<td>437</td>
<td>361</td>
<td>802</td>
<td>808</td>
<td>1,578</td>
<td>37</td>
<td>456,103</td>
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<td>1-3 years</td>
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<td>232</td>
<td>649</td>
<td>819</td>
<td>1,175</td>
<td>368</td>
<td>2,532,201</td>
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<td>315</td>
<td>794</td>
<td>922</td>
<td>1,319</td>
<td>213</td>
<td>2,336,873</td>
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<tr>
<td>7-10 years</td>
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<td>323</td>
<td>828</td>
<td>985</td>
<td>1,767</td>
<td>164</td>
<td>2,808,756</td>
</tr>
<tr>
<td>11-14 years</td>
<td>538</td>
<td>361</td>
<td>1,099</td>
<td>1,420</td>
<td>2,192</td>
<td>148</td>
<td>2,896,893</td>
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<tr>
<td>15-19 years</td>
<td>665</td>
<td>468</td>
<td>1,503</td>
<td>1,777</td>
<td>3,149</td>
<td>163</td>
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<tr>
<td>20-24 years</td>
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<td>2,343</td>
<td>3,126</td>
<td>179</td>
<td>5,089,216</td>
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<tr>
<td>25-54 years</td>
<td>822</td>
<td>621</td>
<td>1,773</td>
<td>1,981</td>
<td>3,786</td>
<td>1,174</td>
<td>28,487,354</td>
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<tr>
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<td>910</td>
<td>785</td>
<td>1,766</td>
<td>2,074</td>
<td>2,548</td>
<td>302</td>
<td>4,655,131</td>
</tr>
<tr>
<td>Males (all)</td>
<td>749</td>
<td>523</td>
<td>1,626</td>
<td>2,097</td>
<td>3,781</td>
<td>1,505</td>
<td>26,298,392</td>
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<tr>
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<td>317</td>
<td>805</td>
<td>1,012</td>
<td>1,397</td>
<td>48</td>
<td>575,019</td>
</tr>
<tr>
<td>1-10 years</td>
<td>365</td>
<td>266</td>
<td>767</td>
<td>847</td>
<td>1,685</td>
<td>376</td>
<td>3,755,220</td>
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<tr>
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<td>464</td>
<td>1,423</td>
<td>1,822</td>
<td>2,802</td>
<td>144</td>
<td>2,969,950</td>
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<td>845</td>
<td>592</td>
<td>1,774</td>
<td>2,303</td>
<td>3,855</td>
<td>937</td>
<td>18,998,203</td>
</tr>
<tr>
<td>Females (all)</td>
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<td>1,893</td>
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<td>1,573</td>
<td>31,018,414</td>
</tr>
<tr>
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<td>428</td>
<td>895</td>
<td>896</td>
<td>1,301</td>
<td>40</td>
<td>419,351</td>
</tr>
<tr>
<td>1-10 years</td>
<td>375</td>
<td>289</td>
<td>765</td>
<td>993</td>
<td>1,347</td>
<td>369</td>
<td>3,922,610</td>
</tr>
<tr>
<td>11-19 years</td>
<td>544</td>
<td>357</td>
<td>1,116</td>
<td>1,537</td>
<td>3,143</td>
<td>167</td>
<td>3,455,377</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>819</td>
<td>690</td>
<td>1,747</td>
<td>1,975</td>
<td>3,060</td>
<td>997</td>
<td>23,221,076</td>
</tr>
<tr>
<td>Lactating women</td>
<td>749</td>
<td>608</td>
<td>1,144</td>
<td>1,223</td>
<td>1,286</td>
<td>7</td>
<td>278,308</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>891</td>
<td>683</td>
<td>1,910</td>
<td>1,957</td>
<td>2,198</td>
<td>27</td>
<td>698,645</td>
</tr>
<tr>
<td>Women aged 15-44 years</td>
<td>766</td>
<td>592</td>
<td>1,598</td>
<td>1,922</td>
<td>3,093</td>
<td>611</td>
<td>16,279,438</td>
</tr>
</tbody>
</table>

TABLE B-6  Estimated Average Daily Water Ingestion (mL/day) from Other Sources (e.g., Wells and Cisterns) During 1994-1996, by People Who Consume Water from Those Sources

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>965</td>
<td>739</td>
<td>1,971</td>
<td>2,475</td>
<td>3,820</td>
<td>2,129</td>
<td>34,693,744</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>306</td>
<td>188</td>
<td>637</td>
<td>754</td>
<td>878</td>
<td>15</td>
<td>117,444</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>265</td>
<td>172</td>
<td>552</td>
<td>560</td>
<td>567</td>
<td>14</td>
<td>198,639</td>
</tr>
<tr>
<td>1-3 years</td>
<td>347</td>
<td>291</td>
<td>710</td>
<td>761</td>
<td>1,190</td>
<td>206</td>
<td>1,243,498</td>
</tr>
<tr>
<td>4-6 years</td>
<td>390</td>
<td>285</td>
<td>778</td>
<td>1,057</td>
<td>1,332</td>
<td>137</td>
<td>1,382,002</td>
</tr>
<tr>
<td>7-10 years</td>
<td>485</td>
<td>399</td>
<td>992</td>
<td>1,093</td>
<td>1,623</td>
<td>134</td>
<td>2,121,832</td>
</tr>
<tr>
<td>11-14 years</td>
<td>733</td>
<td>553</td>
<td>1,561</td>
<td>1,884</td>
<td>3,086</td>
<td>121</td>
<td>2,243,452</td>
</tr>
<tr>
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<td>395</td>
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<td>1,721</td>
<td>2,409</td>
<td>109</td>
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<tr>
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<td>472</td>
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<td>1,648</td>
<td>1,937</td>
<td>67</td>
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</tr>
<tr>
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<td>917</td>
<td>2,175</td>
<td>2,684</td>
<td>4,728</td>
<td>731</td>
<td>15,480,754</td>
</tr>
<tr>
<td>55-64 years</td>
<td>1,276</td>
<td>1,110</td>
<td>2,365</td>
<td>2,916</td>
<td>5,152</td>
<td>272</td>
<td>3,504,576</td>
</tr>
<tr>
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<td>1,259</td>
<td>1,188</td>
<td>2,136</td>
<td>2,470</td>
<td>3,707</td>
<td>323</td>
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</tr>
<tr>
<td>Males (all)</td>
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<td>785</td>
<td>2,107</td>
<td>2,821</td>
<td>4,734</td>
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<tr>
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<td>148</td>
<td>554</td>
<td>567</td>
<td>773</td>
<td>16</td>
<td>198,829</td>
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<tr>
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<td>320</td>
<td>884</td>
<td>1,077</td>
<td>1,630</td>
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<td>2,566,652</td>
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<tr>
<td>11-19 years</td>
<td>702</td>
<td>564</td>
<td>1,366</td>
<td>1,753</td>
<td>2,787</td>
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<td>2,011,715</td>
</tr>
<tr>
<td>≥20 years</td>
<td>1,212</td>
<td>1,001</td>
<td>2,286</td>
<td>3,017</td>
<td>4,883</td>
<td>777</td>
<td>13,103,334</td>
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<tr>
<td>Females (all)</td>
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<td>710</td>
<td>1,826</td>
<td>2,225</td>
<td>3,035</td>
<td>974</td>
<td>16,813,214</td>
</tr>
<tr>
<td>&lt;1 year</td>
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<td>256</td>
<td>537</td>
<td>579</td>
<td>759</td>
<td>13</td>
<td>117,254</td>
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<tr>
<td>1-10 years</td>
<td>416</td>
<td>352</td>
<td>865</td>
<td>1,039</td>
<td>1,615</td>
<td>218</td>
<td>2,180,680</td>
</tr>
<tr>
<td>11-19 years</td>
<td>624</td>
<td>406</td>
<td>1,394</td>
<td>1,873</td>
<td>2,489</td>
<td>127</td>
<td>2,604,579</td>
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<td>≥20 years</td>
<td>1,046</td>
<td>941</td>
<td>1,925</td>
<td>2,371</td>
<td>3,123</td>
<td>616</td>
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<tr>
<td>Lactating women</td>
<td>1,248</td>
<td>915</td>
<td>2,148</td>
<td>2,410</td>
<td>2,620</td>
<td>7</td>
<td>182,414</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>1,066</td>
<td>660</td>
<td>1,676</td>
<td>1,807</td>
<td>3,374</td>
<td>7</td>
<td>168,433</td>
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<tr>
<td>Women aged 15-44 years</td>
<td>904</td>
<td>666</td>
<td>1,863</td>
<td>2,319</td>
<td>3,056</td>
<td>283</td>
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### TABLE B-7 Estimated Average Daily Water Ingestion (mL/day) from All Sources During 1994-1996 by Consumers of Water

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>1,241</td>
<td>1,045</td>
<td>2,345</td>
<td>2,922</td>
<td>4,808</td>
<td>15,172</td>
<td>259,972,235</td>
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<td>544</td>
<td>545</td>
<td>947</td>
<td>1,078</td>
<td>1,365</td>
<td>156</td>
<td>1,507,727</td>
</tr>
<tr>
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<td>563</td>
<td>1,130</td>
<td>1,273</td>
<td>1,672</td>
<td>154</td>
<td>1,732,993</td>
</tr>
<tr>
<td>1-3 years</td>
<td>422</td>
<td>351</td>
<td>807</td>
<td>993</td>
<td>1,393</td>
<td>1,814</td>
<td>12,143,483</td>
</tr>
<tr>
<td>4-6 years</td>
<td>548</td>
<td>468</td>
<td>1,019</td>
<td>1,268</td>
<td>2,031</td>
<td>1,193</td>
<td>12,438,322</td>
</tr>
<tr>
<td>7-10 years</td>
<td>608</td>
<td>514</td>
<td>1,131</td>
<td>1,425</td>
<td>2,172</td>
<td>937</td>
<td>15,248,676</td>
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<tr>
<td>11-14 years</td>
<td>815</td>
<td>651</td>
<td>1,625</td>
<td>1,962</td>
<td>3,033</td>
<td>812</td>
<td>15,504,627</td>
</tr>
<tr>
<td>15-19 years</td>
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<td>776</td>
<td>1,897</td>
<td>2,414</td>
<td>4,027</td>
<td>814</td>
<td>17,697,092</td>
</tr>
<tr>
<td>20-24 years</td>
<td>1,283</td>
<td>1,013</td>
<td>2,508</td>
<td>3,632</td>
<td>5,801</td>
<td>678</td>
<td>18,544,787</td>
</tr>
<tr>
<td>25-54 years</td>
<td>1,486</td>
<td>1,273</td>
<td>2,638</td>
<td>3,337</td>
<td>5,259</td>
<td>4,906</td>
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<tr>
<td>≥6 years</td>
<td>1,532</td>
<td>1,378</td>
<td>2,557</td>
<td>2,999</td>
<td>4,395</td>
<td>1,541</td>
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<td>2,483</td>
<td>3,149</td>
<td>5,212</td>
<td>7,689</td>
<td>126,998,276</td>
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<tr>
<td>&lt;1 year</td>
<td>549</td>
<td>538</td>
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<td>1,278</td>
<td>1,567</td>
<td>1,51</td>
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<td>451</td>
<td>1,024</td>
<td>1,254</td>
<td>1,817</td>
<td>1,993</td>
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<td>11-14 years</td>
<td>1,001</td>
<td>761</td>
<td>1,898</td>
<td>2,434</td>
<td>4,011</td>
<td>809</td>
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<td>2,221</td>
<td>2,703</td>
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<td>559</td>
<td>950</td>
<td>1,131</td>
<td>1,654</td>
<td>159</td>
<td>1,680,410</td>
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<tr>
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<td>445</td>
<td>993</td>
<td>1,226</td>
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<td>1,951</td>
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<tr>
<td>11-19 years</td>
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<td>664</td>
<td>1,652</td>
<td>1,955</td>
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<td>817</td>
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</tr>
<tr>
<td>≥20 years</td>
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<td>1,221</td>
<td>2,416</td>
<td>2,928</td>
<td>4,512</td>
<td>4,556</td>
<td>95,645,114</td>
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<tr>
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<td>1,498</td>
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<td>3,767</td>
<td>4,024</td>
<td>41</td>
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<td>1,228</td>
<td>2,339</td>
<td>2,674</td>
<td>3,557</td>
<td>70</td>
<td>1,751,888</td>
</tr>
<tr>
<td>Women aged 15-44 years</td>
<td>1,265</td>
<td>1,065</td>
<td>2,366</td>
<td>2,952</td>
<td>4,821</td>
<td>2,314</td>
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TABLE B-8  Estimated Average Daily Water Ingestion (mL/kg of Body Weight per Day) from Community Sources during 1994-1996, by People Who Consume Water from Community Sources

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
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<td>33</td>
<td>44</td>
<td>79</td>
<td>13,593</td>
<td>236,742,834</td>
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<td>88</td>
<td>85</td>
<td>169</td>
<td>204</td>
<td>240</td>
<td>106</td>
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<td>56</td>
<td>52</td>
<td>116</td>
<td>127</td>
<td>170</td>
<td>128</td>
<td>1,405,128</td>
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<td>20</td>
<td>53</td>
<td>68</td>
<td>112</td>
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<td>45</td>
<td>65</td>
<td>95</td>
<td>1,025</td>
<td>10,751,616</td>
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<tr>
<td>7-10 years</td>
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<td>12</td>
<td>33</td>
<td>39</td>
<td>60</td>
<td>820</td>
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<td>10</td>
<td>27</td>
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<td>54</td>
<td>736</td>
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<td>9</td>
<td>26</td>
<td>32</td>
<td>62</td>
<td>771</td>
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<tr>
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<td>11</td>
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<td>39</td>
<td>80</td>
<td>637</td>
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<tr>
<td>25-54 years</td>
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<td>13</td>
<td>32</td>
<td>40</td>
<td>65</td>
<td>4,512</td>
<td>104,816,948</td>
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<td>14</td>
<td>32</td>
<td>38</td>
<td>58</td>
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<tr>
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<td>13</td>
<td>32</td>
<td>43</td>
<td>81</td>
<td>6,935</td>
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<td>139</td>
<td>175</td>
<td>235</td>
<td>115</td>
<td>1,180,289</td>
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<td>16</td>
<td>43</td>
<td>55</td>
<td>87</td>
<td>1,705</td>
<td>17,865,064</td>
</tr>
<tr>
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<td>27</td>
<td>38</td>
<td>67</td>
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<td>62</td>
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<td>77</td>
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<td>169</td>
<td>203</td>
<td>119</td>
<td>1,259,405</td>
</tr>
<tr>
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<td>17</td>
<td>45</td>
<td>61</td>
<td>98</td>
<td>1,688</td>
<td>16,731,906</td>
</tr>
<tr>
<td>11-19 years</td>
<td>12</td>
<td>9</td>
<td>26</td>
<td>32</td>
<td>48</td>
<td>752</td>
<td>15,031,443</td>
</tr>
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<td>14</td>
<td>33</td>
<td>41</td>
<td>63</td>
<td>4,099</td>
<td>86,643,885</td>
</tr>
<tr>
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<td>20</td>
<td>54</td>
<td>55</td>
<td>57</td>
<td>33</td>
<td>940,375</td>
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<td>33</td>
<td>43</td>
<td>47</td>
<td>65</td>
<td>1,645,365</td>
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<tr>
<td>Women aged 15-44 years</td>
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<td>12</td>
<td>32</td>
<td>39</td>
<td>66</td>
<td>2,126</td>
<td>54,000,618</td>
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</table>

TABLE B-9 Estimated Average Daily Water Ingestion (mL/kg of Body Weight per Day) from All Sources During 1994-1996 by Consumers of Water

<table>
<thead>
<tr>
<th>Population</th>
<th>Mean</th>
<th>50th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
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<td>17</td>
<td>38</td>
<td>50</td>
<td>87</td>
<td>14,726</td>
<td>253,667,688</td>
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<td>169</td>
<td>196</td>
<td>239</td>
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<td>74</td>
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<td>51</td>
<td>68</td>
<td>97</td>
<td>1,732</td>
<td>11,556,872</td>
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<td>44</td>
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<td>873</td>
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<td>14</td>
<td>33</td>
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<td>48</td>
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<td>67</td>
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<td>50</td>
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<td>158</td>
<td>170</td>
<td>200</td>
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<td>11-19 years</td>
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<td>56</td>
<td>798</td>
<td>16,038,142</td>
</tr>
<tr>
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<td>18</td>
<td>37</td>
<td>45</td>
<td>69</td>
<td>4,421</td>
<td>92,737,736</td>
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<tr>
<td>Lactating women</td>
<td>28</td>
<td>25</td>
<td>53</td>
<td>57</td>
<td>70</td>
<td>40</td>
<td>1,141,186</td>
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<td>Pregnant women</td>
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<td>19</td>
<td>39</td>
<td>44</td>
<td>61</td>
<td>69</td>
<td>1,729,947</td>
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<tr>
<td>Women aged 15-44 years</td>
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<td>16</td>
<td>36</td>
<td>46</td>
<td>77</td>
<td>2,258</td>
<td>57,164,907</td>
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</table>

they are appropriate for the present purpose of estimating the range of current exposures to fluoride. These estimates are based on a 2-day average, whereas for fluoride exposure, long-term averages of intake are usually more important. However, given the size of the population sampled, the likelihood that the entire sample represents days of unusually high or unusually low water intake is small. Thus, these values are considered reasonable indicators both of typical water consumption and of the likely range of water consumption from various sources on a long-term basis. However, they should not be used by themselves to estimate the number of individuals or percentage of the population that consumes a given amount of water on a long-term basis, especially not at the extremes of the range. Water intakes at the low end are not of major importance for the present report, and water intakes at the high end are considered separately (Chapter 2), with additional information beyond what is provided by EPA.

It may be helpful to compare the water intakes (all sources, Table B-7) with values for adequate intake\(^3\) (AI) of water recently published by the Institute of Medicine (IOM 2004; Table B-10). The AI for total water (drinking water, other beverages, and moisture contained in food) is set “to prevent deleterious, primarily acute, effects of dehydration, which include metabolic and functional abnormalities” (IOM 2004). “Given the extreme variability in water needs which are not solely based on differences in metabolism, but also in environmental conditions and activity, there is not a single level of water intake that would ensure adequate hydration and optimal health for half\(^4\) of all apparently healthy persons in all environmental conditions” (IOM 2004). The AI for total water is based on the median total water intake from U.S. survey data (NHANES III, 1988-1994; described by IOM 2004). Daily consumption below the AI is not necessarily a concern “because a wide range of intakes is compatible with normal hydration. Higher intakes of total water will be required for those who are physically active or who are exposed to [a] hot environment” (IOM 2004). For the intake values shown in Table B-10, approximately 80% of the intake comes from drinking water and other beverages (including caffeinated and alcoholic beverages).

Use of bottled water in the United States has at least doubled since 1990 (Grossman 2002), suggesting that more people use bottled water now than in 1994-1996 and/or that individuals use more bottled water per person.

---

\(^3\) “Adequate intake” is defined as “the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate—used when an RDA [recommended dietary allowance] cannot be determined” (IOM 2004).

\(^4\) The estimated average requirement (EAR) on which a recommended dietary allowance is based is defined as “the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group” (IOM 2004).
TABLE B-10 Adequate Intake Values (L/day) for Total Water

<table>
<thead>
<tr>
<th>Group</th>
<th>Males From Foods</th>
<th>Males From Beverages</th>
<th>Males Total Water</th>
<th>Females From Foods</th>
<th>Females From Beverages</th>
<th>Females Total Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>0</td>
<td>0.7</td>
<td>0.7</td>
<td>0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>7-12 months</td>
<td>0.2</td>
<td>0.6</td>
<td>0.8</td>
<td>0.2</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>1-3 years</td>
<td>0.4</td>
<td>0.9</td>
<td>1.3</td>
<td>0.4</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>4-8 years</td>
<td>0.5</td>
<td>1.2</td>
<td>1.7</td>
<td>0.5</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td>9-13 years</td>
<td>0.6</td>
<td>1.8</td>
<td>2.4</td>
<td>0.5</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>14-18 years</td>
<td>0.7</td>
<td>2.6</td>
<td>3.3</td>
<td>0.5</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>&gt;19 years</td>
<td>0.7</td>
<td>3.0</td>
<td>3.7</td>
<td>0.5</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Pregnancy*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.7</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Lactation*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.7</td>
<td>3.1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*Women aged 14-50 years.


However, total water consumption per person from all sources combined probably has not changed substantially. Information for a few groups in the tables (children < 1 year of age, pregnant and lactating women) is based on relatively small sample sizes, and the confidence to be placed in specific percentile values is therefore lower. Sample sizes for some other population subgroups of potential interest (e.g., Native Americans with traditional lifestyles, people in hot climates, people with high physical activity, people with certain medical conditions) were not large enough to evaluate intake by members of the subgroup, although some people from those groups are included in the overall sample (EPA 2000a).

Tables B-11 to B-14 summarize fluoride intakes that would result from ingestion of community water (for the mean, 90th, 95th, and 99th percentiles of consumption estimated by EPA) at various levels of water fluoride (“optimal” fluoridation levels of 0.7, 1.0, or 1.2 mg/L, and the present secondary MCL [SMCL] and MCL of 2 and 4 mg/L, respectively). The SMCL and MCL are included for purposes of comparison; most people in the Unites States do not drink water with those fluoride levels. An average consumer below the age of 6 months would have an intake of 0.06-0.1 mg/kg/day from fluoridated water (0.7-1.2 mg/L), whereas an adult would ingest approximately 0.01-0.02 mg/kg/day. Individuals at the upper levels of water intake from EPA’s estimates (Table B-14) could have fluoride intakes in excess of 1 mg/day at the lowest levels of fluoridation up to about 6 mg/day for some adults, depending on age and level of water fluoridation. Persons in the high-water-intake groups described above could have even higher intakes.
### TABLE B-11 Estimated Intake of Fluoride from Community Water for Average Consumers$^a$

<table>
<thead>
<tr>
<th>Population</th>
<th>Water Intake, mL/day</th>
<th>Fluoride Level</th>
<th>Intake, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.7 mg/L</td>
<td>1 mg/L</td>
</tr>
<tr>
<td>All consumers</td>
<td>1,000</td>
<td>0.70</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>529</td>
<td>0.37</td>
<td>0.53</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>502</td>
<td>0.35</td>
<td>0.50</td>
</tr>
<tr>
<td>1-3 years</td>
<td>351</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>4-6 years</td>
<td>454</td>
<td>0.32</td>
<td>0.45</td>
</tr>
<tr>
<td>7-10 years</td>
<td>485</td>
<td>0.34</td>
<td>0.49</td>
</tr>
<tr>
<td>11-14 years</td>
<td>641</td>
<td>0.45</td>
<td>0.64</td>
</tr>
<tr>
<td>15-19 years</td>
<td>817</td>
<td>0.57</td>
<td>0.82</td>
</tr>
<tr>
<td>20-24 years</td>
<td>1,033</td>
<td>0.72</td>
<td>1.03</td>
</tr>
<tr>
<td>25-54 years</td>
<td>1,171</td>
<td>0.82</td>
<td>1.17</td>
</tr>
<tr>
<td>55-64 years</td>
<td>1,242</td>
<td>0.87</td>
<td>1.24</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1,242</td>
<td>0.87</td>
<td>1.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Water Intake, mL/kg/day</th>
<th>Intake, mg per kg body weight/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>17</td>
<td>0.012</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>88</td>
<td>0.062</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>56</td>
<td>0.039</td>
</tr>
<tr>
<td>1-3 years</td>
<td>26</td>
<td>0.018</td>
</tr>
<tr>
<td>4-6 years</td>
<td>23</td>
<td>0.016</td>
</tr>
<tr>
<td>7-10 years</td>
<td>16</td>
<td>0.011</td>
</tr>
<tr>
<td>11-14 years</td>
<td>13</td>
<td>0.009</td>
</tr>
<tr>
<td>15-19 years</td>
<td>12</td>
<td>0.008</td>
</tr>
<tr>
<td>20-24 years</td>
<td>15</td>
<td>0.011</td>
</tr>
<tr>
<td>25-54 years</td>
<td>16</td>
<td>0.011</td>
</tr>
<tr>
<td>55-64 years</td>
<td>17</td>
<td>0.012</td>
</tr>
<tr>
<td>≥65 years</td>
<td>18</td>
<td>0.013</td>
</tr>
</tbody>
</table>

$^a$Based on water consumption rates estimated by EPA (2000a).

## EXPOSURES FROM FLUORINATED ANESTHETICS

The sampled data in Table B-15 illustrate wide ranges of reported mean peak serum fluoride concentrations from the use of fluorinated anesthetics under various surgical conditions and for different age groups ranging from 22-day-old infants to people > 70 years old. These data are collected from studies conducted in many countries, including Australia, France, Finland, Germany, Ireland, Japan, the United Kingdom, and the United States. The
minimum alveolar concentration per hour (MAC-hr) ranged from short-term (e.g., for cesarean section as reported by Abboud et al. 1989) to prolonged (e.g., >10 hours as reported by Murray et al. 1992 and Obata et al. 2000) surgery and up to 7 days of continuous exposure for critically ill patients (e.g., as reported by Osborne et al. 1996). Test subjects included healthy males who underwent 3-9 hours of anesthesia (Munday et al. 1995), female smokers (Laisalmi et al. 2003), infants and children (age as indicated

**TABLE B-12** Estimated Intake of Fluoride from Community Water for 90th Percentile Consumers

<table>
<thead>
<tr>
<th>Population</th>
<th>Water Intake, mL/day</th>
<th>Fluoride Level 0.7 mg/L</th>
<th>Fluoride Level 1 mg/L</th>
<th>Fluoride Level 1.2 mg/L</th>
<th>Fluoride Level 2 mg/L</th>
<th>Fluoride Level 4 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>2,069</td>
<td>1.45</td>
<td>2.07</td>
<td>2.48</td>
<td>4.14</td>
<td>8.28</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>943</td>
<td>0.66</td>
<td>0.94</td>
<td>1.13</td>
<td>1.89</td>
<td>3.77</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>950</td>
<td>0.67</td>
<td>0.95</td>
<td>1.14</td>
<td>1.90</td>
<td>3.80</td>
</tr>
<tr>
<td>1-3 years</td>
<td>719</td>
<td>0.50</td>
<td>0.72</td>
<td>0.86</td>
<td>1.44</td>
<td>2.88</td>
</tr>
<tr>
<td>4-6 years</td>
<td>940</td>
<td>0.66</td>
<td>0.94</td>
<td>1.13</td>
<td>1.88</td>
<td>3.76</td>
</tr>
<tr>
<td>7-10 years</td>
<td>995</td>
<td>0.70</td>
<td>1.00</td>
<td>1.19</td>
<td>1.99</td>
<td>3.98</td>
</tr>
<tr>
<td>11-14 years</td>
<td>1,415</td>
<td>0.99</td>
<td>1.42</td>
<td>1.70</td>
<td>2.83</td>
<td>5.66</td>
</tr>
<tr>
<td>15-19 years</td>
<td>1,669</td>
<td>1.17</td>
<td>1.67</td>
<td>2.00</td>
<td>3.34</td>
<td>6.68</td>
</tr>
<tr>
<td>20-24 years</td>
<td>2,175</td>
<td>1.52</td>
<td>2.18</td>
<td>2.61</td>
<td>4.35</td>
<td>8.70</td>
</tr>
<tr>
<td>25-54 years</td>
<td>2,326</td>
<td>1.63</td>
<td>2.33</td>
<td>2.79</td>
<td>4.65</td>
<td>9.30</td>
</tr>
<tr>
<td>55-64 years</td>
<td>2,297</td>
<td>1.61</td>
<td>2.30</td>
<td>2.76</td>
<td>4.59</td>
<td>9.19</td>
</tr>
<tr>
<td>≥65 years</td>
<td>2,190</td>
<td>1.53</td>
<td>2.19</td>
<td>2.63</td>
<td>4.38</td>
<td>8.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Water Intake, mL/kg/day</th>
<th>Intake, mg per kg body weight/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>33</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>169</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>116</td>
</tr>
<tr>
<td>1-3 years</td>
<td>53</td>
</tr>
<tr>
<td>4-6 years</td>
<td>45</td>
</tr>
<tr>
<td>7-10 years</td>
<td>33</td>
</tr>
<tr>
<td>11-14 years</td>
<td>27</td>
</tr>
<tr>
<td>15-19 years</td>
<td>26</td>
</tr>
<tr>
<td>20-24 years</td>
<td>31</td>
</tr>
<tr>
<td>25-54 years</td>
<td>32</td>
</tr>
<tr>
<td>55-64 years</td>
<td>32</td>
</tr>
<tr>
<td>≥65 years</td>
<td>32</td>
</tr>
</tbody>
</table>

*aBased on water consumption rates estimated by EPA (2000a).
## TABLE B-13 Estimated Intake of Fluoride from Community Water for 95th Percentile Consumers

<table>
<thead>
<tr>
<th>Population</th>
<th>Water Intake, mL/day</th>
<th>Fluoride Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.7 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intake, mg/day</td>
</tr>
<tr>
<td>All consumers</td>
<td>2,600</td>
<td>1.82</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>1,064</td>
<td>0.74</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>1,122</td>
<td>0.79</td>
</tr>
<tr>
<td>1-3 years</td>
<td>952</td>
<td>0.67</td>
</tr>
<tr>
<td>4-6 years</td>
<td>1,213</td>
<td>0.85</td>
</tr>
<tr>
<td>7-10 years</td>
<td>1,241</td>
<td>0.87</td>
</tr>
<tr>
<td>11-14 years</td>
<td>1,742</td>
<td>1.22</td>
</tr>
<tr>
<td>15-19 years</td>
<td>2,159</td>
<td>1.51</td>
</tr>
<tr>
<td>20-24 years</td>
<td>3,082</td>
<td>2.16</td>
</tr>
<tr>
<td>25-54 years</td>
<td>2,926</td>
<td>2.05</td>
</tr>
<tr>
<td>55-64 years</td>
<td>2,721</td>
<td>1.90</td>
</tr>
<tr>
<td>≥65 years</td>
<td>2,604</td>
<td>1.82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Water Intake, mL/kg/day</th>
<th>Intake, mg per kg body weight/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All consumers</td>
<td>44</td>
<td>0.031</td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>204</td>
<td>0.143</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>127</td>
<td>0.098</td>
</tr>
<tr>
<td>1-3 years</td>
<td>68</td>
<td>0.048</td>
</tr>
<tr>
<td>4-6 years</td>
<td>65</td>
<td>0.046</td>
</tr>
<tr>
<td>7-10 years</td>
<td>39</td>
<td>0.027</td>
</tr>
<tr>
<td>11-14 years</td>
<td>36</td>
<td>0.025</td>
</tr>
<tr>
<td>15-19 years</td>
<td>32</td>
<td>0.022</td>
</tr>
<tr>
<td>20-24 years</td>
<td>39</td>
<td>0.027</td>
</tr>
<tr>
<td>25-54 years</td>
<td>40</td>
<td>0.028</td>
</tr>
<tr>
<td>55-64 years</td>
<td>38</td>
<td>0.027</td>
</tr>
<tr>
<td>≥65 years</td>
<td>37</td>
<td>0.026</td>
</tr>
</tbody>
</table>

*Based on water consumption rates estimated by EPA (2000a).

In Table B-15, and patients with renal insufficiency (Conzen et al. 1995). In general, higher MAC-hr resulted in higher peak serum inorganic fluoride concentration. None of the studies presented in Table B-15 shows clear evidence of renal impairment as a result of the increased serum fluoride concentration, except transient reduction in renal function among the elderly (>70 years) reported by Hase et al. (2000). Higher peak serum concentration...
### TABLE B-14 Estimated Intake of Fluoride from Community Water for 99th Percentile Consumers

- **Population** | **Water Intake, mL/day** | **Fluoride Level.** | **Intake, mg/day** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.7 mg/L</td>
<td>1 mg/L</td>
<td>1.2 mg/L</td>
</tr>
<tr>
<td>All consumers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 year</td>
<td>1,366</td>
<td>0.96</td>
<td>1.37</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>1,529</td>
<td>1.07</td>
<td>1.53</td>
</tr>
<tr>
<td>1-3 years</td>
<td>1,387</td>
<td>0.97</td>
<td>1.39</td>
</tr>
<tr>
<td>4-6 years</td>
<td>1,985</td>
<td>1.39</td>
<td>1.99</td>
</tr>
<tr>
<td>7-10 years</td>
<td>1,999</td>
<td>1.40</td>
<td>2.00</td>
</tr>
<tr>
<td>11-14 years</td>
<td>2,564</td>
<td>1.79</td>
<td>2.56</td>
</tr>
<tr>
<td>15-19 years</td>
<td>3,863</td>
<td>2.70</td>
<td>3.86</td>
</tr>
<tr>
<td>20-24 years</td>
<td>5,356</td>
<td>3.75</td>
<td>5.36</td>
</tr>
<tr>
<td>25-54 years</td>
<td>4,735</td>
<td>3.31</td>
<td>4.74</td>
</tr>
<tr>
<td>55-64 years</td>
<td>4,222</td>
<td>2.96</td>
<td>4.22</td>
</tr>
<tr>
<td>≥65 years</td>
<td>3,668</td>
<td>2.57</td>
<td>3.67</td>
</tr>
</tbody>
</table>

Water Intake, mL/kg/day | Intake, mg per kg body weight/day

<table>
<thead>
<tr>
<th></th>
<th>0.055</th>
<th>0.079</th>
<th>0.095</th>
<th>0.158</th>
<th>0.316</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 year</td>
<td>0.168</td>
<td>0.240</td>
<td>0.288</td>
<td>0.480</td>
<td>0.960</td>
</tr>
<tr>
<td>0.5-0.9 year</td>
<td>0.119</td>
<td>0.170</td>
<td>0.204</td>
<td>0.340</td>
<td>0.680</td>
</tr>
<tr>
<td>1-3 years</td>
<td>0.078</td>
<td>0.112</td>
<td>0.134</td>
<td>0.224</td>
<td>0.448</td>
</tr>
<tr>
<td>4-6 years</td>
<td>0.067</td>
<td>0.095</td>
<td>0.114</td>
<td>0.190</td>
<td>0.380</td>
</tr>
<tr>
<td>7-10 years</td>
<td>0.042</td>
<td>0.060</td>
<td>0.072</td>
<td>0.120</td>
<td>0.240</td>
</tr>
<tr>
<td>11-14 years</td>
<td>0.038</td>
<td>0.054</td>
<td>0.065</td>
<td>0.108</td>
<td>0.216</td>
</tr>
<tr>
<td>15-19 years</td>
<td>0.043</td>
<td>0.062</td>
<td>0.074</td>
<td>0.124</td>
<td>0.248</td>
</tr>
<tr>
<td>20-24 years</td>
<td>0.056</td>
<td>0.080</td>
<td>0.096</td>
<td>0.160</td>
<td>0.320</td>
</tr>
<tr>
<td>25-54 years</td>
<td>0.066</td>
<td>0.085</td>
<td>0.078</td>
<td>0.130</td>
<td>0.260</td>
</tr>
<tr>
<td>55-64 years</td>
<td>0.041</td>
<td>0.058</td>
<td>0.070</td>
<td>0.116</td>
<td>0.232</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.037</td>
<td>0.053</td>
<td>0.064</td>
<td>0.106</td>
<td>0.212</td>
</tr>
</tbody>
</table>

*Based on water consumption rates estimated by EPA (2000a).*

was reported for smokers (Cousins et al. 1976; Laisalmi et al. 2003) and is associated with alcohol, obesity, and multiple drug use (Cousins et al. 1976). Because the reference point for the potential nephrotoxicity in these studies was the peak serum fluoride concentration, data are generally not available for an estimation of the total fluoride load or the area under the curve from the use of these anesthetics.
<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Baseline</th>
<th>Peak</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoflurane</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 years</td>
<td>13</td>
<td>NA</td>
<td>NA</td>
<td>No change</td>
<td>Hara et al. 1998</td>
</tr>
<tr>
<td>NA</td>
<td>90</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>Groudine et al. 1999</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>6</td>
<td>3.7</td>
<td>NA</td>
<td>4</td>
<td>Hase et al. 2000</td>
</tr>
<tr>
<td>55.5 years</td>
<td>26</td>
<td>NA</td>
<td>about 2.5</td>
<td>5</td>
<td>Goldberg et al. 1996</td>
</tr>
<tr>
<td>57 years</td>
<td>24</td>
<td>1.1</td>
<td>3.8</td>
<td>5.4</td>
<td>Newman et al. 1994</td>
</tr>
<tr>
<td>28 years</td>
<td>11</td>
<td>9.2</td>
<td>&lt;2</td>
<td>5.5</td>
<td>Higuchi et al. 1995</td>
</tr>
<tr>
<td>28 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>0.06</td>
<td>5.6</td>
<td>5.6</td>
<td>Abboud et al. 1989</td>
</tr>
<tr>
<td>27.7 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>0.14</td>
<td>5.9</td>
<td>5.6</td>
<td>Abboud et al. 1989</td>
</tr>
<tr>
<td>48.5 years</td>
<td>20</td>
<td>15.9</td>
<td>NA</td>
<td>7.4</td>
<td>Obata et al. 2000</td>
</tr>
<tr>
<td>53.7 years</td>
<td>7</td>
<td>4.8</td>
<td>NA</td>
<td>8</td>
<td>Matsumura et al. 1994</td>
</tr>
<tr>
<td>26-54 years</td>
<td>5</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1-2.4</td>
<td>8.4-27.9</td>
<td>Osborne et al. 1996</td>
</tr>
<tr>
<td>20-75 years</td>
<td>9</td>
<td>19.2</td>
<td>3.5-3.8</td>
<td>43.2</td>
<td>Murray et al. 1992</td>
</tr>
<tr>
<td><strong>Enflurane</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 days to 11 years</td>
<td>40</td>
<td>0.3-0.7</td>
<td>NA</td>
<td>2-8</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>22 day</td>
<td>1</td>
<td>0.7-1.5</td>
<td>NA</td>
<td>4-10</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>29 day</td>
<td>1</td>
<td>1.5</td>
<td>NA</td>
<td>6-10</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>3 months</td>
<td>1</td>
<td>1.6</td>
<td>NA</td>
<td>7</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>4 months</td>
<td>1</td>
<td>1.6</td>
<td>NA</td>
<td>11</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>9 months</td>
<td>1</td>
<td>2.0</td>
<td>NA</td>
<td>7</td>
<td>Oikkonen and Meretoja 1989</td>
</tr>
<tr>
<td>1-9 years</td>
<td>8</td>
<td>NA</td>
<td>1.7</td>
<td>10.5</td>
<td>Hinkle 1989</td>
</tr>
<tr>
<td>47-60 years</td>
<td>5</td>
<td>4-6.8</td>
<td>about 2-3</td>
<td>7</td>
<td>Sakai and Takaori 1978</td>
</tr>
<tr>
<td>63.9 years</td>
<td>20</td>
<td>1.07</td>
<td>NA</td>
<td>13.3</td>
<td>Conzen et al. 1995</td>
</tr>
<tr>
<td>48 years (27-58 years)</td>
<td>16</td>
<td>1</td>
<td>NA</td>
<td>13.8</td>
<td>Laisalmi et al. 2003</td>
</tr>
</tbody>
</table>

<sup>a</sup>MAC-hour indicates the concentration of the anesthetic agent.

<sup>b</sup>Age data for these patients is not specified.

<sup>c</sup>Baseline fluoride levels for these patients are not specified.
### TABLE B-15

**Serum Inorganic Fluoride Concentration from Fluorinated Anesthetic Agents**

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour</th>
<th>Mean Serum Inorganic Fluoride, m</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 years (35-39 years)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17</td>
<td>1</td>
<td>NA</td>
<td>18.7</td>
</tr>
<tr>
<td>59.3 years</td>
<td>40</td>
<td>2.8</td>
<td>1.2</td>
<td>16.75</td>
</tr>
<tr>
<td>47.8 years</td>
<td>8</td>
<td>1.24</td>
<td>2-2.5</td>
<td>18</td>
</tr>
<tr>
<td>40.2 years</td>
<td>10</td>
<td>2.7</td>
<td>1.8</td>
<td>22.2</td>
</tr>
<tr>
<td>18-35 years</td>
<td>5</td>
<td>6</td>
<td>NA</td>
<td>28.1</td>
</tr>
<tr>
<td>18-35 years</td>
<td>5</td>
<td>NA</td>
<td>27.5</td>
<td></td>
</tr>
</tbody>
</table>

**Isoflurane**

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour</th>
<th>Mean Serum Inorganic Fluoride, m</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>51 years</td>
<td>13</td>
<td>NA</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>6</td>
<td>3.7</td>
<td>NA</td>
<td>about 2.5</td>
</tr>
<tr>
<td>55.5 years</td>
<td>26</td>
<td>NA</td>
<td>about 2.5</td>
<td></td>
</tr>
<tr>
<td>57 years</td>
<td>24</td>
<td>1.1</td>
<td>3.8</td>
<td>5.4</td>
</tr>
<tr>
<td>28 years</td>
<td>11</td>
<td>9.2</td>
<td>&lt;2</td>
<td>5.5</td>
</tr>
<tr>
<td>28 years</td>
<td>20</td>
<td>0.06</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>27.7 years</td>
<td>20</td>
<td>0.14</td>
<td>5.9</td>
<td>5.6</td>
</tr>
<tr>
<td>48.5 years</td>
<td>20</td>
<td>15.9</td>
<td>NA</td>
<td>7.4</td>
</tr>
<tr>
<td>53.7 years</td>
<td>7</td>
<td>4.8</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>26-54 years</td>
<td>5</td>
<td>NA</td>
<td>2.1-2.4</td>
<td>8.4-27.9</td>
</tr>
<tr>
<td>20-75 years</td>
<td>9</td>
<td>19.2</td>
<td>3.5-3.8</td>
<td>43.2</td>
</tr>
</tbody>
</table>

**Enflurane**

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour</th>
<th>Mean Serum Inorganic Fluoride, m</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 days to 11 years</td>
<td>40</td>
<td>0.3-0.7</td>
<td>NA</td>
<td>2-8</td>
</tr>
<tr>
<td>6.2 years (1-12 years)</td>
<td>40</td>
<td>0.7-1.5</td>
<td>NA</td>
<td>4-10</td>
</tr>
<tr>
<td>42-57 years</td>
<td>5</td>
<td>2.9-4.9</td>
<td>2-3</td>
<td>3</td>
</tr>
<tr>
<td>50 years</td>
<td>8</td>
<td>2.5</td>
<td>2-2.5</td>
<td>4</td>
</tr>
<tr>
<td>28.9 years</td>
<td>20</td>
<td>0.07</td>
<td>5.9</td>
<td>5.6</td>
</tr>
<tr>
<td>9.2 years (5-12 years)</td>
<td>25</td>
<td>2.2</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>20-75 years</td>
<td>10</td>
<td>19.5</td>
<td>3.8</td>
<td>12.6</td>
</tr>
</tbody>
</table>

**Halothane**

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour</th>
<th>Mean Serum Inorganic Fluoride, m</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>41.5 years</td>
<td>10</td>
<td>4.9</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>6.2 years (1-12 years)</td>
<td>40</td>
<td>2.6</td>
<td>NA</td>
<td>1.8</td>
</tr>
<tr>
<td>42-57 years</td>
<td>5</td>
<td>2.9-4.9</td>
<td>2-3</td>
<td>3</td>
</tr>
<tr>
<td>50 years</td>
<td>8</td>
<td>2.5</td>
<td>2-2.5</td>
<td>4</td>
</tr>
<tr>
<td>28.9 years</td>
<td>20</td>
<td>0.07</td>
<td>5.9</td>
<td>5.6</td>
</tr>
<tr>
<td>9.2 years (5-12 years)</td>
<td>25</td>
<td>2.2</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>20-75 years</td>
<td>10</td>
<td>19.5</td>
<td>3.8</td>
<td>12.6</td>
</tr>
</tbody>
</table>

**Sevoflurane**

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour</th>
<th>Mean Serum Inorganic Fluoride, m</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months (7.7-25 months)</td>
<td>41</td>
<td>4.7</td>
<td>NA</td>
<td>13.8</td>
</tr>
<tr>
<td>6.2 years (1-12 years)</td>
<td>40</td>
<td>2.6</td>
<td>NA</td>
<td>14.7</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>7</td>
<td>5.1</td>
<td>NA</td>
<td>18</td>
</tr>
<tr>
<td>8.8 years</td>
<td>25</td>
<td>2.2</td>
<td>NA</td>
<td>21</td>
</tr>
<tr>
<td>50 years</td>
<td>25</td>
<td>0.8</td>
<td>3.8</td>
<td>23</td>
</tr>
<tr>
<td>67.4 years</td>
<td>21</td>
<td>1.01</td>
<td>NA</td>
<td>2.5</td>
</tr>
<tr>
<td>60.5 years</td>
<td>40</td>
<td>2.9</td>
<td>1.2</td>
<td>27.7</td>
</tr>
<tr>
<td>52.7 years</td>
<td>24</td>
<td>NA</td>
<td>about 2.5</td>
<td>28</td>
</tr>
<tr>
<td>18-35 years</td>
<td>5</td>
<td>3</td>
<td>NA</td>
<td>30.5</td>
</tr>
<tr>
<td>18-35 years</td>
<td>5</td>
<td>6</td>
<td>NA</td>
<td>31-34</td>
</tr>
<tr>
<td>18-35 years</td>
<td>5</td>
<td>9</td>
<td>NA</td>
<td>36.6</td>
</tr>
<tr>
<td>29 years</td>
<td>15</td>
<td>9.9</td>
<td>&lt;2</td>
<td>36.8</td>
</tr>
<tr>
<td>53 years</td>
<td>13</td>
<td>3.7</td>
<td>NA</td>
<td>about 31</td>
</tr>
<tr>
<td>NA</td>
<td>98</td>
<td>2.9</td>
<td>NA</td>
<td>40</td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th>Age (range)</th>
<th>No. of Subjects</th>
<th>MAC-hour(^a)</th>
<th>Mean Serum Inorganic Fluoride, (\mu M)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.6 years (19-49 years)</td>
<td>11</td>
<td>10.6</td>
<td>NA</td>
<td>41.9</td>
</tr>
<tr>
<td>56.8 years</td>
<td>10</td>
<td>18.0 high flow</td>
<td>NA</td>
<td>47.1</td>
</tr>
<tr>
<td>62.0 years</td>
<td>10</td>
<td>16.7 low flow</td>
<td>NA</td>
<td>53.5</td>
</tr>
<tr>
<td>54.9 years</td>
<td>8</td>
<td>6.1</td>
<td>NA</td>
<td>54</td>
</tr>
<tr>
<td>24 years</td>
<td>8</td>
<td>14.0</td>
<td>&lt;2</td>
<td>57.5</td>
</tr>
</tbody>
</table>

\(^a\)MAC is the minimum alveolar concentration, or the mean end-tidal anesthetic concentration. When MAC-hr is not reported, it is estimated as MAC-hr = (mean percent concentration) \(\times\) (anesthesia time).

\(^b\)Cesarean section patients with induction to delivery time of 7.4-8.4 minutes.

\(^c\)Critically ill patients under anesthesia for 5-7 days at 0.6-1.2% isoflurane.

\(^d\)Smoking > 10 cigarettes a day.

ABBREVIATION: NA, not applicable.
TABLE B-16 Summary of Estimated Safe and Adequate Daily Dietary Intakes\(^a\) of Fluoride

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Weight, kg(^b)</th>
<th>Range, mg/day</th>
<th>Range, mg/kg/day(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>6</td>
<td>0.1-0.5</td>
<td>0.017-0.083</td>
</tr>
<tr>
<td>0.5-1</td>
<td>9</td>
<td>0.2-1.0</td>
<td>0.022-0.11</td>
</tr>
<tr>
<td>1-3</td>
<td>13</td>
<td>0.5-1.5</td>
<td>0.038-0.12</td>
</tr>
<tr>
<td>4-6</td>
<td>20</td>
<td>1.0-2.5</td>
<td>0.050-0.13</td>
</tr>
<tr>
<td>7-10</td>
<td>28</td>
<td>1.5-2.5</td>
<td>0.054-0.089</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>45</td>
<td>1.5-2.5(^d)</td>
<td>0.033-0.056</td>
</tr>
<tr>
<td>15-18</td>
<td>66</td>
<td>1.5-2.5(^d)</td>
<td>0.023-0.038</td>
</tr>
<tr>
<td>19-24</td>
<td>72</td>
<td>1.5-4.0(^e)</td>
<td>0.021-0.056</td>
</tr>
<tr>
<td>25-50</td>
<td>79</td>
<td>1.5-4.0</td>
<td>0.019-0.051</td>
</tr>
<tr>
<td>51+</td>
<td>77</td>
<td>1.5-4.0</td>
<td>0.019-0.052</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>46</td>
<td>1.5-2.5</td>
<td>0.033-0.054</td>
</tr>
<tr>
<td>15-18</td>
<td>55</td>
<td>1.5-2.5(^d)</td>
<td>0.027-0.045</td>
</tr>
<tr>
<td>19-24</td>
<td>58</td>
<td>1.5-4.0(^e)</td>
<td>0.026-0.069</td>
</tr>
<tr>
<td>25-50</td>
<td>63</td>
<td>1.5-4.0</td>
<td>0.024-0.063</td>
</tr>
<tr>
<td>51+</td>
<td>65</td>
<td>1.5-4.0</td>
<td>0.023-0.062</td>
</tr>
</tbody>
</table>

\(^a\)The term “safe and adequate daily dietary intake” was used by the NRC (1989b) “when data were sufficient to estimate a range of requirements, but insufficient for developing a Recommended Dietary Allowance.” This category was to be accompanied by “the caution that upper levels in the safe and adequate range should not be habitually exceeded because the toxic level for many trace elements may be only several times usual intakes.” Use of this term should not be taken to imply that the present committee considers these intakes to be safe or adequate.

\(^b\)Median for age group.

\(^c\)Calculated from range (mg/day) and weight (kg) given for age groups.

\(^d\)Upper limit for children and adolescents (upper age not specified).

\(^e\)Upper limit for adults.


REFERENCE INTAKES OF FLUORIDE

Table B-16 provides the median weight and range of fluoride intake (mg/day; safe and adequate daily dietary intake\(^5\)), by age group, from the National Research Council (NRC 1989b). Table B-17 provides the reference

\(^5\)The term “safe and adequate daily dietary intake” was used by the NRC (1989b) “when data were sufficient to estimate a range of requirements, but insufficient for developing a Recommended Dietary Allowance.” This category was to be accompanied by “the caution that upper levels in the safe and adequate range should not be habitually exceeded because the toxic level for many trace elements may be only several times usual intakes.” Use of this
TABLE B-17 Summary of Dietary Reference Intakes of Fluoride

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Reference Weight, kg</th>
<th>Adequate Intake mg/d</th>
<th>mg/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Tolerable Upper Intake mg/d</th>
<th>mg/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>7</td>
<td>0.01</td>
<td>0.0014</td>
<td>0.7</td>
<td>0.10</td>
</tr>
<tr>
<td>0.5-1</td>
<td>9</td>
<td>0.5</td>
<td>0.056</td>
<td>0.9</td>
<td>0.10</td>
</tr>
<tr>
<td>1-3</td>
<td>13</td>
<td>0.7</td>
<td>0.054</td>
<td>1.3</td>
<td>0.10</td>
</tr>
<tr>
<td>4-8</td>
<td>22</td>
<td>1</td>
<td>0.045</td>
<td>2.2</td>
<td>0.10</td>
</tr>
<tr>
<td>9-13</td>
<td>40</td>
<td>2</td>
<td>0.050</td>
<td>10</td>
<td>0.25</td>
</tr>
<tr>
<td>Boys 14-18</td>
<td>64</td>
<td>3</td>
<td>0.047</td>
<td>10</td>
<td>0.16</td>
</tr>
<tr>
<td>Girls 14-18</td>
<td>57</td>
<td>3</td>
<td>0.053</td>
<td>10</td>
<td>0.18</td>
</tr>
<tr>
<td>Males 19+</td>
<td>76</td>
<td>4</td>
<td>0.053</td>
<td>10</td>
<td>0.13</td>
</tr>
<tr>
<td>Females 19+</td>
<td>61</td>
<td>3</td>
<td>0.049</td>
<td>10</td>
<td>0.16</td>
</tr>
</tbody>
</table>

<sup>a</sup>Calculated from intake (mg/day) and weight (kg) given for age groups by IOM (1997) and ADA (2005).


weight and range of fluoride intake (mg/day; dietary reference intake), by age group, from the Institute of Medicine (IOM 1997) and the American Dental Association (ADA 2005). In both tables, the intakes in terms of mg/kg/day were calculated from the cited information as indicated.

Term should not be taken to imply that the present committee considers these intakes to be safe or adequate.
APPENDIX C

Ecologic and Partially Ecologic Studies in Epidemiology

Individual-level studies collect information on outcome, exposure, and covariates (potential confounders and effect modifiers) for each individual. Ecologic studies collect information about groups. Partially ecologic studies use a combination of individual-level and group-level variables.

The goal of most ecologic studies is to make inferences about individuals based on aggregated data. Unfortunately, severe bias can occur. (Bias in this context means systematic errors in the results of the analysis; it does not impugn the integrity or intention of the researchers). Ecologic bias has several sources (Greenland 1992; Greenland and Robins 1994; Morgenstern 1998; Webster 2000):

- Nondifferential exposure misclassification within groups (which tends to bias results away from the null)
- Confounding within and between groups
- Effect measure modification within and between groups
- Misspecification error when model is nonlinear
- Inadequate control of covariates
- Magnification of bias by aggregation due to confounding by group and effect measure modification by group
- Failure to weight by population
- Failure to standardize both outcome and exposure in the same way.

Instead of simply dismissing all ecologic studies as unreliable, it is preferable to estimate the direction and magnitude of potential biases. Quantify-
ing bias in ecologic studies is quite difficult in practice. Nevertheless, certain design features tend to reduce ecologic bias, including the following:

1. Studies with outcome variables that can be modeled with weighted or ordinary least-squares regression (e.g., bone fluoride levels) are generally preferable to those with binary outcomes or rates, commonly modeled with logistic or log-linear regression. Nonlinear ecologic models can induce bias due to misspecification.

2. Exposure variables that are continuous on the individual-level before aggregation are generally preferable to those that are dichotomous (aggregation of dichotomous exposures typically produces variables of the form “fraction exposed”). The latter can be subject to nondifferential exposure misclassification within groups, tending to bias ecologic studies away from the null; they also tend to increase the amount of bias magnification. In contrast, using of the average exposure within each group need not cause measurement error on the ecologic level, a special case of the Berkson error model. Errors of this type produce unbiased results in ordinary linear regression; in log-linear regression, bias also depends on variance of the errors.

3. Exposure should be as uniform as possible within groups but as different as possible between groups.

4. Avoid, if possible, confounders with highly nonlinear relationships to outcome, because these can be very difficult to control in ecologic studies.

The following two types of partially ecologic studies are often used in epidemiology.

1. Multilevel models typically supplement individual-level variables with contextual variables. The latter are intrinsically group-level variables that have no real counterpart on the individual-level, (e.g., herd immunity or income inequality).

2. Studies that measure outcome and covariates at the individual level, but exposure at the group level, are commonly used in environmental and occupational epidemiology. This design is sometimes called “semi-individual.” For example, fluoride concentrations might be measured in the water system serving a community. Everyone in that group is assigned the same exposure. Exposure is an aggregated variable, not an intrinsically group-level variable. Feasibility is the typical reason for using this design; individual exposure measurements are typically expensive and time-consuming, if they are possible at all.

The semi-individual kind of partially ecologic study can be thought of as individual-level with exposure measurement error. Unfortunately, semi-individual studies are not necessarily free of ecologic bias. Suppose the
ecologic exposure variable is the fraction exposed in the group (aggregated from dichotomous exposures at the individual level). Nondifferential exposure misclassification within groups tends to produce bias away from the null as in ecologic studies. Although bias magnification (see list above) can occur, the amount of bias tends to be intermediate between a fully ecologic study and a fully individual study (at least in certain cases that have been analyzed). Because covariate information is collected at the individual level, the ability to control for confounding can be much better than with purely ecologic studies. For more discussions of these issues, see Webster (2000, 2002) and Björk and Strömberg (2002).

In sum, semi-individual studies are generally more trustworthy than fully ecologic studies. Studies using exposure variables based on continuous individual-level exposures are preferable to those based on dichotomous individual-level exposures.
In healthy young and middle-aged adult humans, fasting plasma fluoride concentrations (expressed as micromoles per liter [$\mu$mol/L]) are thought to be approximately equal to concentrations in water (expressed as parts per million [ppm] or milligrams per liter [mg/L]) provided that water is the major source of chronic exposure (NRC 1993; Whitford 1996). Dunipace et al. (1995) exposed weanling male Sprague-Dawley rats to fluoride in water plus a low-fluoride diet for 18 months. Plasma fluoride concentrations increased up to 3 months and remained fairly constant afterward. Plasma levels ($\mu$mol/L) were three to seven times less than water concentrations (ppm or mg/L) at several different concentrations and time points. In another chronic experiment with Sprague-Dawley rats, plasma/water fluoride ratios decreased from 4.2 at 2 months to 1.5 at 18 months (Whitford and Birdsong-Whitford 2000; G. Whitford, University of Georgia, personal communication, June 2, 2004). The reason for the difference between the experiments is unclear. Dunipace et al. (1995) concluded that rats require about five times greater water concentrations than humans to reach the same plasma concentration. That factor appears uncertain, in part because the ratio can change with age or length of exposure. In addition, this approach compares water concentrations, not dose. Plasma levels can also vary considerably both between people and in the same person over time (Ekstrand 1978).

Comparing bone fluoride levels in a 16-week rat experiment with human data from Zipkin et al. (1958), Turner et al. (1992) estimated that “humans incorporate fluoride ~18 times more readily than rats when the
rats are on a normal calcium diet.” The comparison was based on water fluoride concentrations.

Several longer-term animal experiments are compared in Table D-1. The National Toxicology Program (NTP) (Bucher et al. 1991) and Maurer et al. (1990) experiments are well-known long-term fluoride carcinogenicity assays. Of the four studies, Maurer et al. (1990) added fluoride to feed; the others added fluoride to water. Figure D-1 shows results for male rats for the three studies that added fluoride to water. Fluoride bone concentrations for female rats were somewhat higher in the NTP study and somewhat lower in the Maurer et al. study. Femur and vertebra fluoride concentrations were similar in the Dunipace et al. (1995) study. Femur diaphysis fluoride concentrations were similar to concentrations in other sites, except for femur epiphysis, which was higher (Whitford and Birdsong-Whitford 2000; G. Whitford, University of Georgia, personal communication, June 2, 2004). Figure D-1 also shows regression lines through each set of rat data, as well as the crude and adjusted estimates for the human data (Zipkin et al. 1958) discussed earlier. The adjusted line estimates bone concentrations in males with 70 years of residence, but the slope is very similar to the crude model.

Assuming that linear models are realistic in this range and that rats at 18 to 24 months are roughly physiologically comparable to humans at 70 years (Dunipace et al. 1995), the committee compared the slopes for the human and rat studies. The estimates in the left column of Table D-2 (bone versus water) were computed by dividing the slopes for the human data by the slopes estimated for the Dunipace and NTP rat studies. (The commit-

### TABLE D-1 Four Chronic Rat Experiments That Measured Fluoride in Bone

<table>
<thead>
<tr>
<th></th>
<th>Dunipace et al. 1995</th>
<th>NTP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Maurer et al. 1990</th>
<th>Whitford and Birdsong-Whitford 2000&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain</td>
<td>Sprague-Dawley</td>
<td>F344/N</td>
<td>Sprague-Dawley</td>
<td>Sprague-Dawley</td>
</tr>
<tr>
<td>Sampling</td>
<td>3, 6, 12, 18 months</td>
<td>103 weeks</td>
<td>99 weeks</td>
<td>2, 6, 12, 18 months</td>
</tr>
<tr>
<td>Start time</td>
<td>Weanling</td>
<td>Weanling</td>
<td>M, F</td>
<td>M, F</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>0, 11, 45, 79</td>
<td>—</td>
<td>1, 10, 100</td>
</tr>
<tr>
<td>Water fluoride, mg/L</td>
<td>0, 5, 15, 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet fluoride, ppm</td>
<td>≤1.2</td>
<td>8</td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>Bone samples</td>
<td>Femur, vertebra</td>
<td>Humerus</td>
<td>Radius, ulna</td>
<td>Femur, radius, calvarium</td>
</tr>
</tbody>
</table>

<sup>a</sup>The NTP results were published by Bucher et al. (1991).

<sup>b</sup>Data are available only in abstract form; unpublished data provided by G. Whitford, University of Georgia, personal communication, June 2, 2004.
FIGURE D-1 Comparison of bone concentrations in humans and rats on the basis of drinking water concentration

Male rats: NTP (humerus), Whitford (femur diaphysis), Dunipace (femur). Zipkin data: Regression results from crude and adjusted model, the latter assuming males and 70 years residency.

Regression results:
Dunipace: \( y = 625 + 147x \) \( (r^2 = 0.97) \)
NTP: \( y = 443 + 63.1x \) \( (r^2 = 0.99) \)
Human (crude): \( y = 517 + 1,549x \)
Human (adjusted to male, 70 years residence): \( y = 1,300 + 1,527x \)

tee also estimated two slopes for the human data, crude and adjusted for length of residency and sex. The crude and adjusted estimates are similar, barely changing the ratios in Table D-2.) These results suggest that rats require water concentrations 10 to 20 times higher than humans to achieve comparable bone fluoride concentrations.

Why are the Dunipace bone concentrations larger than the NTP results? As shown in Table D-1, the NTP study was longer and had higher fluoride concentrations in feed, but both of those factors should increase bone concentrations. The use of different rat strains could contribute to the difference. Type of bone is unlikely to explain the difference. Even if water concentrations are the same, doses might be different. The NTP study provided estimates of average absorbed fluoride doses (assuming 100% from water, 60% from feed) of 0.2, 0.8, 2.5, and 4.1 mg/kg/day for the four experimental groups. Using data provided by Dunipace et al. (1995), the committee estimates average fluoride doses of 0.042, 0.34, 0.96, and 2.83
TABLE D-2 Comparative Uptake of Fluoride Between Humans and Rats

<table>
<thead>
<tr>
<th></th>
<th>Bone Versus Water</th>
<th>Bone Versus Dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zipkin/NTP</td>
<td>24 to 25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42</td>
</tr>
<tr>
<td>Zipkin/Dunipace</td>
<td>10 to 11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
</tr>
<tr>
<td>Zipkin/Maurer</td>
<td>NA</td>
<td>40</td>
</tr>
</tbody>
</table>

<sup>a</sup>Use of the crude and adjusted human models produces very similar results (difference of less than 1).

<sup>b</sup>The lower value uses the adjusted human model (male, 70 years residency); the higher value uses the crude human model.

mg/kg/day for the four experimental groups (divide fluoride intake, µg/day, by body weight for each water concentration and each time interval: 3, 6, 12, and 18 months). At each water concentration, the doses decrease over time. Compute the time-weighted average dose. That does not account for absorption, but feed intake is a small fraction of the total, especially for higher doses. Figure D-2 plots the average doses versus bone fluoride for both studies. Use of average dose reduces the difference in slopes between the Dunipace and NTP studies but not very much. Dunipace et al. found that bone fluoride concentrations increased very rapidly in the first 3 months, followed by a slow increase. As a result, average dose might not be the best metric. On the basis of water consumption rates, exposures appear similar at 3 months (C. Turner, Indiana University, personal communication). Calcium concentrations in feed were higher in the NTP study (0.6 ppm) than in the Dunipace study (0.5 ppm), reducing fluoride absorption (C. Turner, Indiana University, personal communication). The slope estimated for the Maurer data lies between the other two, but the results of this experiment appear to be nonlinear.

To estimate dose for the Zipkin data, the committee assumed the same water consumption (2 L/day) and body weight (70 kg) for every subject, based on standard the U.S. Environmental Protection Agency figures. This assumption multiplies the slope calculated earlier by a constant, 70/2.

The right-hand column of Table D-2 compares human and rat fluoride uptake on an average dose basis. The ratio of the slopes has increased to 20 to 40. The ratios would be higher if a smaller water consumption rate for humans had been assumed. The very high bone concentration predicted by Rao et al. (1995) for women exposed to fluoride in drinking water at 4 mg/L for 70 years suggests an even higher ratio.

Because many assumptions were involved in estimating the values presented in Table D-2, they should be used with caution. But values support a rat-to-human conversion factor for bone fluoride uptake of at least an order of magnitude.
FIGURE D-2 Comparison of bone concentrations in humans and rats on the basis of estimated dose.

To keep the results visible, the figure omits the high data point from Maurer et al. (11.3 mg of fluoride/kg/day, 16,760 mg/kg ash).

Male rats: NTP (humerus), Dunipace (femur), Maurer (radius and ulna). Zipkin data: Regression results from crude and adjusted model, the latter assuming males and 70 years residency.

Regression results:
- Dunipace: \( y = 415 + 2,664x \) (\( r^2 = 0.98 \))
- NTP: \( y = 145 + 1,283x \) (\( r^2 = 0.99 \))
- Maurer: \( y = 1,911 + 1,345x \) (\( r^2 = 0.98 \))
- Human (crude): \( y = 517 + 1,549(70/2)x \)
- Human (adjusted to male, 70 years residence): \( y = 1,300 + 1,527(70/2)x \)
APPENDIX
E

Detailed Information on Endocrine Studies of Fluoride

The tables that follow contain detailed information on the endocrine studies discussed in Chapter 8, including study design, exposure information, and reported effects. Exposure conditions and duration and fluoride concentrations are provided as given in the published articles. Many of the tables include estimates of exposure in units of mg/kg/day to aid in comparing studies. When possible, these estimates were made from information (e.g., intake rate of drinking water, body weight) given in the articles. Where such information was not available in a published article, the assumptions used to make the estimates are listed in footnotes to the tables. Note that for most of the human studies, the exposure estimates (mg/kg/day) are for typical or average values for the groups and do not reflect the full range of likely exposures.
### TABLE E-1 Effects of Fluoride on Thyroid Follicular Cell Function in Experimental Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Fluoride Concentration or Dose</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (Hebrew University albino, males; infants at start, 30-32 g) See also Table E-16</td>
<td>Drinking water 0.55, 1, or 10 mg/L (0.055, 0.1, and 1 mg/kg/day)</td>
<td>9 months</td>
<td>No significant differences in basal metabolic ratio, thyroid weight, radioiodine uptake, total blood iodine, protein-bound iodine, or urinary excretion. TSH not measured.</td>
<td>Gedalia et al. 1960</td>
<td></td>
</tr>
<tr>
<td>Rats (females, 180-230 g)</td>
<td>Gastric tube 0.2 or 2.2 µg/day iodine in diet</td>
<td>750 µg/day in 1 mL water (3.3-4.2 mg/kg/day)</td>
<td>2 months</td>
<td>No effect of fluoride on body weight, weight of thyroid, total composition of iodinated amino acids, or amount of iodide present in the thyroid. No effect of fluoride on iodine excretion in the higher-iodine group. Decreased protein-bound iodine, T3, and T4 (low-iodine group). Decreased biogenesis of T3 and T4 following administration of 131I (low- and high-iodine groups). TSH not measured.</td>
<td>Stolc and Podoba 1960</td>
</tr>
<tr>
<td>Rats (Wistar, males; initial weight 170-230 g; 13 per group)</td>
<td>Drinking water 0, 0.1, or 1 mg/day Dietary iodine, 0.45 µg/g feed (0.45 ppm)</td>
<td>60 days</td>
<td>Decreased plasma T3 and T4, decreased free T4 index, increased T3-resin uptake (all changes statistically significant except for the decrease in T3 for the group receiving 0.1 mg/day) TSH not measured.</td>
<td>Bobek et al. 1976</td>
<td></td>
</tr>
</tbody>
</table>

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Fluoride in Drinking Water: A Scientific Review of EPA’s Standards

http://www.nap.edu/catalog/11571.html
<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Exposed</th>
<th>Effects Reference</th>
</tr>
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<tbody>
<tr>
<td>Rats (Hebrew University albino, males; infants at start, 30-32 g)</td>
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<td>2 months</td>
<td>No effect of fluoride on body weight, weight of thyroid, total composition of iodinated amino acids, or amount of protein-bound iodine, T3 and T4 (low-iodine group). Decreased biogenesis of T3 and T4 following administration of 131I (low- and high-iodine groups). TSH not measured. Stolc and Podoba 1960</td>
</tr>
<tr>
<td>Rats (Wistar, males; initial weight 170-230 g; 13 per group)</td>
<td>Drinking water, Dietary iodine, 0.45 µg/g feed (0.45 ppm), 0, 0.1, or 1 mg/day (0, 0.43-0.59, or 4.3-5.9 mg/kg/day)</td>
<td>60 days</td>
<td>Decreased plasma T3 and T4, decreased free T4 index, increased T3-resin uptake (all changes statistically significant except for the decrease in T3 for the group receiving 0.1 mg/day)</td>
</tr>
<tr>
<td>Cows (Holstein; various states of lactation, 9-13 cows from each of 9 herds)</td>
<td>Feed supplements, 1-22 mg/kg F in feed (estimated) (approximate doses, 0.03-0.7 mg/kg/day)</td>
<td>Chronic</td>
<td>Urinary fluoride ≥ 2.9 mg/L (range 1.04-15.7 mg/L, average 5.13 mg/L). Decreased T3, T4, cholesterol and increased eosinophils with increasing urinary fluoride (adjusted for stage of lactation); serum calcium correlated with T3 and T4. Fluorosis herds (S1, C4, V3, B2) had lower T4 than herds W, B, M, G (P &lt; 0.05). Feeding of iodinated casein to herd B2 for 3 weeks resulted in 100% increase in milk production, increased hematopoiesis, reduced eosinophils, increased serum calcium, decreased serum phosphorus, and increase in serum T4 from 3.4 to 14.1 μg/dL. TSH not measured. Bone fluoride: mean, 2,400 ppm in ash (range, 850-6,935, 22 specimens from 8 herds). Feeding of iodinated casein to herd B2 for 3 weeks resulted in 100% increase in milk production, increased hematopoiesis, reduced eosinophils, increased serum calcium, decreased serum phosphorus, and increase in serum T4 from 3.4 to 14.1 μg/dL. TSH not measured. Bone fluoride: mean, 2,400 ppm in ash (range, 850-6,935, 22 specimens from 8 herds). Elevated T3 and T4 in rats on 1 mg/L in drinking water and low-fluoride diet. Low T3 and normal T4 in rats on 1, 5, or 10 mg/L in drinking water and high-fluoride diet. Decreased TSH and GH in animals receiving 100 or 200 mg/L in drinking water. Full details not available. Hillman et al. 1979</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Fluoride Concentration or Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (Wistar, 3-month-old, 200-400 g)</td>
<td>Drinking water Animals were kept 21 days on a diet containing 0.15% PTU to deplete their thyroid glands of iodine and thyro-globulin. For the next 2 days, a low-iodine diet (0.04 μg/g) was fed, but no more PTU. During the next 6 days the rats were given sufficient iodine (1.5 μg of iodide/mL of drinking water, labeled with 0.1 μCi of 125I). Then fluoride was given as indicated.</td>
<td>60 or 200 mg/L (6-20 mg/kg/day)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 days</td>
<td>Serum fluoride at end of experiment (μg/mL): 0.165 (controls), 0.246 (60 mg/L), and 0.576 (200 mg/L). No significant differences from control values for relative thyroid weight, iodine content of thyroglobulin, thyroidal content of organic iodine, or amounts of monoiodotyrosine, diiodotyrosine, T3, and T4. TSH not measured.</td>
<td>Siebenhüner et al. 1984</td>
</tr>
<tr>
<td>Cows (Holstein, females; age 5-6 months at start, 30 animals total)</td>
<td>NaF added to feed Iodine intake not stated, presumably adequate</td>
<td>30 or 50 ppm in feed</td>
<td>Data reported through age 100 weeks</td>
<td>Serum fluoride at age 88 weeks (mg/L): 0.06 (controls), 0.20 (30 ppm in feed), and 0.28 (50 ppm in feed). Urinary fluoride at age 88 weeks (mg/L): 0.05 (controls), 0.1 (30 ppm in feed), and 0.12 (50 ppm in feed). No significant differences from control values for T4 concentration and T3 uptake at ages 40, 56, 72, and 88 weeks.</td>
<td>Clay and Suttie 1987</td>
</tr>
<tr>
<td>Rats (Wistar, males and females; 120 ± 19 g at start, 212 animals total)</td>
<td>Drinking water Low or normal iodine</td>
<td>10 or 30 mg/L in drinking water (1 or 3 mg/kg/day)</td>
<td>7 months 10 mg/L and normal iodine: no significant effect (some decrease in serum T4 and T3). 30 mg/L and normal iodine: statistically significant decreases in T4, T3, thyroid peroxidase, 131I uptake, [3H]-leucine uptake, and thyroid weight. 10 mg/L and low iodine: abnormalities in thyroid function beyond those attributable to low iodine; reduced thyroid peroxidase; low T4, without compensatory transformation of T4 to T3. TSH not measured.</td>
<td>Guan et al. 1988</td>
<td></td>
</tr>
<tr>
<td>Species and Strain</td>
<td>Exposure Conditions</td>
<td>Fluoride Concentration or Dose</td>
<td>Data reported through</td>
<td>Effects</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
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<tr>
<td>Rats (Wistar, 3-month-old, 200-400 g)</td>
<td>Drinking water</td>
<td>60 or 200 mg/L (6-20 mg/kg/day)</td>
<td>Serum fluoride at end of experiment (µg/mL): 0.165 (controls), 0.246 (60 mg/L), and 0.576 (200 mg/L).</td>
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<tr>
<td>Cows (Holstein, females; age 5-6 months at start, 30 animals total)</td>
<td>NaF added to feed</td>
<td>30 or 50 ppm in feed</td>
<td>Urinary fluoride at age 88 weeks (mg/L): 1 (controls), 13 (30 ppm in feed), and 20 (50 ppm in feed). Bone fluoride at age 17 months (ppm in tail vertebra, means of groups of 5 animals): 352 and 453 (controls), 2,306 and 2,712 (30 ppm in feed), and 3,539 and 3,946 (50 ppm in feed). No significant differences from control values for T4 concentration and T3 uptake at ages 40, 56, 72, and 88 weeks.</td>
<td>TSH not measured.</td>
<td>Clay and Suttie 1987</td>
</tr>
<tr>
<td>Rats (Wistar, males and females; 120 ± 19 g at start, 212 animals total)</td>
<td>Drinking water</td>
<td>10 or 30 mg/L in drinking water (1 or 3 mg/kg/day)</td>
<td>10 mg/L and normal iodine: no significant effect (some decrease in serum T4 and T3). 30 mg/L and normal iodine: statistically significant decreases in T4, T3, thyroid peroxidase, $^{131}$I uptake, [³H]-leucine uptake, and thyroid weight. 10 mg/L and low iodine: abnormalities in thyroid function beyond those attributable to low iodine; reduced thyroid peroxidase; low T4, without compensatory transformation of T4 to T3.</td>
<td>TSH not measured.</td>
<td>Guan et al. 1988</td>
</tr>
</tbody>
</table>

continued
### TABLE E-1 Continued

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Fluoride Concentration or Dose$^a$</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (Kunmin, males; 288 animals in 9 groups of 32 each; 13-15 g at start)</td>
<td>Drinking water (NaF) Iodine: low (0 µg/L); normal (20 µg/L); excess 2500 µg/L) Low-iodine, low-fluoride chow fed to all groups.</td>
<td>Low, 0 mg/L; normal, 0.6 mg/L; excess, 30 mg/L (0, 0.06, and 3 mg/kg/day)$^b$</td>
<td>100 or 150 days</td>
<td>For iodine-excess groups, thyroid weight relative to body weight decreased significantly with increasing fluoride intake. For iodine-deficient groups, goiter incidence at 100 days was 18%, 40%, and 66% for low-, normal-, and high-fluoride groups, respectively; at 150 days, goiter incidence was 81-100%. Fluoride-excess groups at 100 days had elevated T4 with all concentrations of iodine intake and elevated T3 for iodine-deficient animals. Fluoride excess significantly inhibited radiiodine uptake in iodine-deficient and iodine-normal groups. Incisor fluorosis occurred only in the fluoride excess groups; severity was greater in the iodine-deficient animals. Bone fluoride in fluoride-excess animals was greater in iodine-deficient (means, 2,560-2,880 ppm ash) or iodine-excess animals (means, 2,140-2,380 ppm ash) than in iodine-normal animals (means, 1,830-2,100 ppm ash). TSH not measured.</td>
<td>Zhao et al. 1998</td>
</tr>
<tr>
<td>cattle near aluminum smelter in India</td>
<td>Contaminated pasture from smelter emissions No information on iodine intake</td>
<td>Not available</td>
<td>Not available</td>
<td>Prevalence of enamel fluorosis up to 75% (adult buffalo), 70% (adult cattle), or 100% (calves), depending on location; histological changes in teeth and skeletal and enamel fluorosis. Significantly decreased concentrations of calcium and phosphorus in blood and inorganic phosphorus, and creatinine. Urinary fluoride averaged 26.5 mg/L close to smelter. Full details not available.</td>
<td>Swarup et al. 1998</td>
</tr>
<tr>
<td>cattle, buffaloes, sheep, and goats in 21 villages in India (286 calves, 1,675 adult cattle, 290 adult buffaloes, 780 goats, 564 sheep)</td>
<td>Drinking water No information on iodine intake</td>
<td>1.5-4 mg/L in drinking water</td>
<td>Native livestock present in relevant area since birth</td>
<td>Prevalence of enamel fluorosis up to 75% (adult buffalo), 70% (adult cattle), or 100% (calves), depending on location; histological changes in teeth and skeletal and enamel fluorosis. Significantly decreased concentrations of calcium and phosphorus in blood and inorganic phosphorus, and creatinine. Urinary fluoride averaged 26.5 mg/L close to smelter. Full details not available.</td>
<td>Choubisa 1999</td>
</tr>
<tr>
<td>Mice (Wistar, adult females; about 30 g at beginning; fluoride was administered during pregnancy and lactation)</td>
<td>Drinking water (Iodine intake 0.720 ± 0.12 µg/g in diet)</td>
<td>500 mg/L in drinking water (50 mg/kg/day to the mothers)</td>
<td>From day 15 of pregnancy to day 14 of lactation</td>
<td>Body weight of pups at 14 days old was reduced 35%; 75% decrease in plasma T4 in pups; 17% decrease in cerebral protein in pups; histological changes in cerebellum in pups. TSH not measured.</td>
<td>Trabelsi et al. 2001</td>
</tr>
<tr>
<td>Species and Strain</td>
<td>Exposure Conditions</td>
<td>Fluoride Concentration or Dose</td>
<td>Exposure Duration</td>
<td>Effects</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cattle near aluminum smelter in India</td>
<td>Contaminated pasture from smelter emissions</td>
<td>Not available</td>
<td>Not available</td>
<td>Skeletal and enamel fluorosis (58% of animals within 3 km of plant were affected). Significantly decreased concentrations of T3. Significantly increased concentrations of alkaline phosphatase, inorganic phosphorus, and creatinine. Urinary fluoride averaged 26.5 mg/L close to smelter.</td>
<td>Swarup et al. 1998</td>
</tr>
<tr>
<td>Cattle, buffaloes, sheep, and goats in 21 villages in India (286 calves, 1,675 adult cattle, 290 adult buffaloes, 780 goats, 564 sheep)</td>
<td>Drinking water</td>
<td>1.5-4 mg/L in drinking water</td>
<td>Native livestock present in relevant area since birth</td>
<td>Prevalence of enamel fluorosis up to 75% (adult buffalo), 70% (adult cattle), or 100% (calves), depending on location; prevalence of skeletal fluorosis up to 37.5% (buffalo) or 29% (cattle), depending on location; no evidence of enamel or skeletal fluorosis in goats or sheep. No clinical evidence of goiter in any fluorotic animals. Animals not showing clinical signs of fluorosis were not examined for goiter. No measurements of any thyroid hormone parameters or TSH.</td>
<td>Choubisa 1999</td>
</tr>
<tr>
<td>Mice (Wistar, adult females; about 30 g at beginning; fluoride was administered during pregnancy and lactation)</td>
<td>Drinking water (Iodine intake 0.720 ± 0.12 µg/g in diet)</td>
<td>500 mg/L in drinking water (50 mg/kg/day to the mothers)</td>
<td>From day 15 of pregnancy to day 14 of lactation</td>
<td>Body weight of pups at 14 days old was reduced 35%; 75% decrease in plasma T4 in pups; 17% decrease in cerebral protein in pups; histological changes in cerebellum in pups. TSH not measured.</td>
<td>Trabelsi et al. 2001</td>
</tr>
</tbody>
</table>

continued
<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Fluoride Concentration or Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows (3 years old with chronic fluorosis, 10 controls without fluorosis, from</td>
<td>Drinking water iodine intakes not</td>
<td>5.7-15.2 mg/L in drinking water</td>
<td>Lifelong</td>
<td>Mean values of T4, T3, and PBI in fluorotic animals were below the normal ranges and also</td>
<td>Cinar and Selcuk</td>
</tr>
<tr>
<td>different regions of Turkey)</td>
<td>specifically stated</td>
<td>(approximate doses, 0.7-1.8 mg/kg/day)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>significantly less than in controls. Low concentrations of bioavailable iodine in fluorosis</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>region might be a factor. TSH not measured.</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Information in parentheses was calculated from information given in the papers or as otherwise noted.

<sup>b</sup>Based on water consumption of about 10% of body weight.

<sup>c</sup>ATSDR (2003) stated that an intermediate-duration minimal risk level (MRL) derived from this study of thyroid effects in rats would have been lower (more protective) than the chronic-duration MRL derived from a human study of bone effects (0.05 mg/kg/day).

<sup>d</sup>Based on feed consumption of 16 kg/day (dry weight) and body weight of 500 kg.

<sup>e</sup>Based on water consumption of about 10% of body weight and feed consumption of about 8% of body weight.

<sup>f</sup>Text says “triiodothyronine uptake” and table says “thyroxine uptake.” Data for different treatment groups were not given.

<sup>g</sup>In many mammalian species, maternal fluoride exposures are not well reflected by fluoride concentrations in milk; therefore, the impacts of fetal exposure and of reduced milk production by the mothers must also be considered.

<sup>h</sup>Based on water consumption of 60 L/day and body weight of 500 kg.

**ABBREVIATIONS:** GH, growth hormone; PBI, protein-bound iodine; TSH, thyroid-stimulating hormone.
TABLE E-2 Summary of Effects of Fluoride Exposure for Rats with Different Amounts of Iodine Intake (Means ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight, g</th>
<th>Urinary Fluoride, mg/L</th>
<th>Urinary Iodine, µg/24 hours</th>
<th>131I Uptake, % at 24 hours</th>
<th>Serum T4, µg/dL</th>
<th>Serum T3, ng/dL</th>
<th>TPO, G.U./100 g of body weight</th>
<th>[3H] Leucine Uptake, cpm/10 mg</th>
<th>Thyroid Weight, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>293 ± 57</td>
<td>1.23 ± 0.22</td>
<td>1.110 ± 0.26</td>
<td>47.37 ± 5.66</td>
<td>3.64 ± 1.45</td>
<td>70.65 ± 30.29</td>
<td>2.04 ± 0.22</td>
<td>1,808 ± 358</td>
<td>9.97 ± 3.52</td>
</tr>
<tr>
<td>2</td>
<td>294 ± 85</td>
<td>6.65 ± 0.91</td>
<td>1.215 ± 0.35</td>
<td>44.74 ± 5.14</td>
<td>3.02 ± 1.48</td>
<td>61.96 ± 26.02</td>
<td>1.98 ± 0.51</td>
<td>1,728 ± 790</td>
<td>9.58 ± 2.40</td>
</tr>
<tr>
<td>3</td>
<td>254 ± 68c</td>
<td>8.16 ± 0.89c</td>
<td>1.150 ± 0.87</td>
<td>42.73 ± 4.31</td>
<td>1.44 ± 0.39c</td>
<td>43.00 ± 11.31</td>
<td>1.73 ± 0.24</td>
<td>1,258 ± 293</td>
<td>7.90 ± 2.37</td>
</tr>
<tr>
<td>4</td>
<td>289 ± 72</td>
<td>1.23 ± 0.26</td>
<td>0.095 ± 0.029</td>
<td>58.40 ± 9.54</td>
<td>0.76 ± 0.70c</td>
<td>95.81 ± 25.18</td>
<td>2.57 ± 0.44c</td>
<td>2,252 ± 683</td>
<td>19.91 ± 11.23</td>
</tr>
<tr>
<td>5</td>
<td>308 ± 63</td>
<td>6.23 ± 0.88c</td>
<td>0.099 ± 0.017c</td>
<td>59.05 ± 7.59c</td>
<td>0.65 ± 0.57c</td>
<td>68.05 ± 21.96</td>
<td>1.75 ± 0.21c</td>
<td>1,804 ± 459</td>
<td>20.13 ± 22.10</td>
</tr>
</tbody>
</table>

*a*Normal iodine: 310 ng/g in diet; 8.2 ng/mL in drinking water.

*b*Fluoride: 1.856 ppm in diet; 0.4 mg/L in drinking water.

*c*P < 0.01, compared with group 1 (control).

*d*Low iodine: 20-62.5 ng/g in diet; deionized drinking water.

*e*Also statistically significant at 2 hours and 6 hours (P < 0.01, compared with group 1).

*f*Fluoride: 1.743 ppm in diet; deionized water.

ABBREVIATIONS: cpm, counts per minute; G.U., guaiacol unit; TPO, thyroid peroxidase.

### TABLE E-3 Summary of Selected Findings for Fluoride-Exposed Dairy Cows

<table>
<thead>
<tr>
<th>Herd</th>
<th>Number Observed</th>
<th>Urinary Fluoride, mg/L&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Serum T4, µg/dL&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Serum T3, ng/dL&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Plasma Calcium, mg/dL&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>12</td>
<td>2.92 ± 0.52</td>
<td>4.60 ± 0.34</td>
<td>175 ± 7.2</td>
<td>10.1 ± 0.15</td>
</tr>
<tr>
<td>B</td>
<td>12</td>
<td>5.37 ± 0.43</td>
<td>4.83 ± 0.19</td>
<td>168 ± 5.8</td>
<td>9.5 ± 0.11</td>
</tr>
<tr>
<td>M</td>
<td>12</td>
<td>6.39 ± 0.92</td>
<td>5.30 ± 0.38</td>
<td>177 ± 8.4</td>
<td>9.6 ± 0.11</td>
</tr>
<tr>
<td>G</td>
<td>12</td>
<td>6.33 ± 0.74</td>
<td>4.82 ± 0.28</td>
<td>159 ± 7.7</td>
<td>9.4 ± 0.15</td>
</tr>
<tr>
<td>P</td>
<td>12</td>
<td>3.47 ± 0.47</td>
<td>—</td>
<td>—</td>
<td>9.3 ± 0.12</td>
</tr>
<tr>
<td>S1</td>
<td>12</td>
<td>6.29 ± 1.08</td>
<td>3.59 ± 0.26</td>
<td>126 ± 8.4</td>
<td>9.1 ± 0.17</td>
</tr>
<tr>
<td>C4</td>
<td>9</td>
<td>—</td>
<td>2.21 ± 0.54</td>
<td>—</td>
<td>9.5 ± 0.14</td>
</tr>
<tr>
<td>V3</td>
<td>10</td>
<td>—</td>
<td>3.35 ± 0.47</td>
<td>—</td>
<td>9.5 ± 0.13</td>
</tr>
<tr>
<td>B2</td>
<td>13</td>
<td>—</td>
<td>3.39 ± 0.42</td>
<td>—</td>
<td>8.9 ± 0.12</td>
</tr>
</tbody>
</table>

<sup>a</sup>Herd identification as reported by Hillman et al. (1979). Enamel fluorosis and elevated bone fluoride were confirmed in herds S1, C4, V3, and B2. Cows were uniformly distributed throughout lactation in all herds.

<sup>b</sup>W < all others (P < 0.05).

<sup>c</sup>C4 < all others; S1, V3, B2 < W, B, M, G (P < 0.05).

<sup>d</sup>S1 < W, B, M, G (P < 0.05).

<sup>e</sup>B2 < M, W; S1, P, G < W (P < 0.05).

<sup>f</sup>—indicates not measured or not reported.

TABLE E-4 Effects of Fluoride in Drinking Water on Thyroid Follicular Cell Function in Humans

<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Fluoride Concentration&lt;sup&gt;a&lt;/sup&gt; and Exposure Duration/Conditions</th>
<th>Iodine Status and Other Information</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, 3 villages, 2,008 persons, all ages</td>
<td>5.4, 6.1, and 10.7 mg/L (means for the villages)</td>
<td>Iodine in drinking water: 14.4-175.3 µg/L (inverse relationship to fluoride concentration). Iodine from salt: 86 µg/day. Calcium in diet: 480 mg/day. Diet considered deficient in proteins, fats, calcium, vitamins A and C.</td>
<td>Transient goiters in persons aged 14-17; associated with increased fluoride in water and with decreased iodine in water.</td>
<td>Siddiqui 1960</td>
</tr>
<tr>
<td>Israel, 2,685 girls, ages 7-18</td>
<td>&lt;0.1-0.9 mg/L</td>
<td>Iodine in drinking water: &lt;2-100 µg/L.</td>
<td>Endemic goiter associated with low iodine content of water, but not with fluoride content of water.</td>
<td>Gedalia and Brand 1963</td>
</tr>
<tr>
<td>U.S., adults ages 18-60; 106 from Crisfield, Maryland (42% female); 109 from New York City (29% female)</td>
<td>0.09 mg/L in New York City 3.48 mg/L in Crisfield, Maryland</td>
<td>General iodine status not given. Chrisfield: the 3 individuals with the highest PBI concentrations were all on iodine medication for non-thyroidal disease, and one of the individuals with the lowest PBI had had a partial thyroidectomy for a thyroid cyst.&lt;sup&gt;b&lt;/sup&gt; New York City: the individual with the highest PBI was taking 3 grains of thyroid daily.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No differences in PBI. No gross thyroid abnormalities or gross evidence for thyroid disease. Mild or moderate enamel fluorosis in 75% of individuals from Crisfield.</td>
<td>Leone et al. 1964</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fluoride concentrations are means for the villages, unless otherwise noted.

<sup>b</sup> Data based on a single subject in each study.
<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Fluoride Concentration and Exposure Duration/Conditions</th>
<th>Iodine Status and Other Information</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal, 648 persons in 13 villages with similar iodine concentrations in water, all ages</td>
<td>&lt; 0.1 to 0.36 mg/L Lifelong</td>
<td>Iodine in drinking water: ≤1 µg/L Diet low in iodine; iodized salt not available. Calcium in water, 3-148 mg/L. Magnesium in water, 0.5-77 mg/L. Water hardness, 10-670 ppm (as CaCO$_3$).</td>
<td>Goiter prevalence (5-69%) positively associated with fluoride concentration ($\rho = 0.74$, $P &lt; 0.01$). Goiter prevalence of at least 20% associated with fluoride concentrations $\geq 0.19$ mg/L. Goiter prevalence also associated positively with water hardness ($\rho = 0.77$, $P &lt; 0.01$), calcium ($\rho = 0.78$, $P &lt; 0.01$) and magnesium ($\rho = 0.83$, $P &lt; 0.01$). Effect of fluoride was independent of that of hardness.</td>
<td>Day and Powell-Jackson 1972</td>
</tr>
<tr>
<td>India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females), mean age 29 years; 5 control individuals (3 males, 2 females), mean age 31 years Case-control study; individual estimates of current fluoride intake, measurements of fasting plasma fluoride and urinary fluoride; incomplete information on selection of subjects and controls</td>
<td>7.8-8.0 or 24.5-25.0 mg/L Current exposure to 0.8 and 1.8 mg/L in water for the 2 persons who had moved Lifelong 2 persons had moved to nonendemic areas 2 or 5 years previously Symptomatic for 10-15 years</td>
<td>Iodine status not given</td>
<td>PBI values all normal (4.2-5.8 µg/100 mL). No evidence of goiter or thyroid dysfunction. See also Tables E-9, E-10, and E-12</td>
<td>Teotia et al. 1978</td>
</tr>
</tbody>
</table>
Study Population(s) and Type
Fluoride Concentration and Exposure Duration/Conditions
Iodine Status and Other Information
Effects Reference

Nepal, 648 persons in 13 villages with similar iodine concentrations in water, all ages
Ecologic study; cross-sectional; ... about one-third of the population in each village (children presenting for inoculations plus accompanying adults)

< 0.1 to 0.36 mg/L
Lifelong

Iodine in drinking water:
≤ 1 µg/L
Diet low in iodine; iodized salt not available.
Calcium in water, 3-148 mg/L.
Magnesium in water, 0.5-77 mg/L.
Water hardness, 10-670 ppm (as CaCO$_3$).

Goiter prevalence (5-69%) positively associated with fluoride concentration ($\rho = 0.74$, $P < 0.01$).
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Effect of fluoride was independent of that of hardness.

Day and Powell-Jackson 1972

India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females), mean age 29 years; 5 control ... of fasting plasma fluoride and urinary fluoride; incomplete information on selection of subjects and controls

7.8-8.0 or 24.5-25.0 mg/L
Current exposure to 0.8 and 1.8 mg/L in water for the 2 persons who had moved
Lifelong
2 persons had moved to nonendemic areas 2 or 5 years previously
Symptomatic for 10-15 years

Iodine status not given
PBI values all normal (4.2-5.8 µg/100 mL).
No evidence of goiter or thyroid dysfunction.
See also Tables E-9, E-10, and E-12

Teotia et al. 1978

Germany, 13-15 years old, males and females, 17 in low-fluoride group and 26 in high-fluoride group
Ecologic exposure measure; cross-sectional; no information on subject selection; 2 of the original 19 in low-fluoride group excluded upon discovery of hyperthyroidism

0.1-0.2 and 3 mg/L
Lifelong
Iodine status not given

No significant differences in T3 uptake, T4, free T4 index, T3, reverse T3, thyroglobulin, TSH, thyroglobulin antibodies, or microsomal thyroid antibodies. Unexplained decrease in thyroglobulin in girls (31.3 ± 12.9 ng/mL in the low-fluoride group and 13.8 ± 4.3 ng/mL in the high-fluoride group); this difference is also reflected in the means for boys and girls combined.

Baum et al. 1981

Ukraine, 13-15 years old, males and females, 17 in low-fluoride group and 26 in high-fluoride group
Ecologic exposure measure; cross-sectional; no information on subject selection

Values not given
Iodine status not given

Iodine deficiency and “adaptive amplification of the hypophyseal-thyroid system” (increased TSH?) in residents with high fluoride in drinking water; increased incidence of “functional disturbance” of the thyroid, but no structural changes. Full details not available.

Baum et al. 1981

Ukraine, 2 cities with different water fluoride concentrations
Ecologic exposure measure; cross-sectional; no information on subject selection

Values not given
Iodine status not given

Iodine deficiency and “adaptive amplification of the hypophyseal-thyroid system” (increased TSH?) in residents with high fluoride in drinking water; increased incidence of “functional disturbance” of the thyroid, but no structural changes. Full details not available.

Sidora et al. 1983

continued
<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Fluoride Concentration(^a) and Exposure Duration/Conditions</th>
<th>Iodine Status and Other Information</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine, 47 healthy persons (ages 19-59), 43 persons with hyperthyroidism (ages 18-58), and 33 persons with hypothyroidism (ages 20-55) Ecologic exposure measure; cross-sectional; no information on subject selection other than by thyroid status See also Table 8-6</td>
<td>Region I: 0.5-1.4 mg/L (mean, 1.0) Region II: 1.6-3.5 mg/L (mean, 2.3) Lifelong (permanent residents)</td>
<td>Iodine status not given</td>
<td>Among normal individuals, significantly increased serum TSH and thyroidal (^{131})I uptake and significantly decreased serum T3 in Region II, although values still within normal ranges. Differences between Regions I and II not seen among thyroidopathy patients. No information on the prevalence of thyroid disease in the two regions.</td>
<td>Bachinskii et al. 1985</td>
</tr>
<tr>
<td>China, children ages 7-14, 250 in Area A and 256 in Area B Ecologic exposure measure; cross-sectional; no information on subject selection</td>
<td>Area A, 0.88 mg/L (enamel fluorosis, 20.80%) Area B, 0.34 mg/L (enamel fluorosis, 16.00%) Lifelong</td>
<td>Iodine in drinking water (µg/L): Area A, 5.21; Area B, 0.96 Goiter prevalence: Area A, 91%; Area B, 82%</td>
<td>Area A had higher TSH, slightly higher (^{131})I uptake, and lower mean IQ than Area B. Area A also had reduced T3 and elevated reverse T3, compared with Area B. Urine fluoride (mg/L): Area A, 2.56; Area B, 1.34-1.61.</td>
<td>Lin et al. 1991</td>
</tr>
<tr>
<td>Country</td>
<td>Age Range</td>
<td>Study Details</td>
<td>Fluoride Concentration</td>
<td>Iodine Status and Other Information</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ukraine</td>
<td>19-59, 18-58</td>
<td>Healthy persons (ages 19-59), 43 persons with hyperthyroidism (ages 18-58), 33 persons with thyroidopathy (ages 18-58)</td>
<td>≥1 mg/L</td>
<td>Iodine status not given; among normal individuals, significantly increased serum TSH and thyroidal 131I uptake and significantly decreased serum T3 in Region II, although values still within normal ranges. Differences between Regions I and II not seen among thyroidopathy patients. No information on the prevalence of thyroid disease in the two regions.</td>
</tr>
<tr>
<td>China</td>
<td>7-14</td>
<td>Children ages 7-14, 250 in Area A and 256 in Area BE</td>
<td>High fluoride, values not given (Enamel fluorosis in children, 72.9%)</td>
<td>High iodine, values not given</td>
</tr>
<tr>
<td>India</td>
<td>All ages</td>
<td>22,276 individuals in a single district, all ages</td>
<td>≥1 mg/L</td>
<td>Enamel fluorosis prevalence ranged from 6.0% to 59.0% (12.2% overall) Lifelong</td>
</tr>
<tr>
<td>China</td>
<td>No details available</td>
<td>Ecologic study; probably cross-sectional; no information on subject selection</td>
<td>High fluoride, values not given (Enamel fluorosis in children, 72.9%)</td>
<td>High iodine, values not given</td>
</tr>
<tr>
<td>India</td>
<td>Adults, children</td>
<td>Ecologic study; cross-sectional; subjects included 1% of total population and 5% of school children of randomly selected villages</td>
<td>Iodine in drinking water ≥ 10 µg/L</td>
<td>Goiter prevalence ranged from 9.5% to 37.5% (14.0% overall) Significant positive correlation between prevalence of goiter and enamel fluorosis ($r = 0.4926$, $P &lt; 0.001$). No significant correlation between water iodine concentration and goiter prevalence ($r = 0.1443$, $P &gt; 0.05$). In regions with water iodine concentrations &gt; 20 µg/L, goiter prevalence was significantly higher in regions with fluoride &gt; 2 mg/L (27.8%) than in regions with fluoride &lt; 2 mg/L (17.1%). No evidence for functional changes in thyroid activity associated with the presence of goiter. Prevalence of thyroid enlargement was 3.8% in adults and 29.8% in children, and of enamel fluorosis, 35.5% and 72.9%, respectively.</td>
</tr>
<tr>
<td>Study Population(s) and Type</td>
<td>Fluoride Concentration(^a) and Exposure Duration/Conditions</td>
<td>Iodine Status and Other Information</td>
<td>Effects</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>India, 500 individuals from 52 villages in 2 districts; blood samples from randomly selected subset of control and fluorotic individuals</td>
<td>1.0-6.53 mg/L (18 villages, &lt;2 mg/L; 26 villages, 2-4 mg/L; 8 villages, &gt;4 mg/L; 74% with slight to severe mottling of teeth) Control, 0.56-0.72 mg/L Lifelong</td>
<td>Iodine status not given</td>
<td>Serum fluoride (mg/L): 38%, &lt;0.2; 47%, 0.2-0.4; 15%, &gt;0.4. Significant increase in serum T4 ((P &lt; 0.001): 14.77 ± 0.512 µg/dL versus 9.16 ± 0.63 µg/dL) (ranges, 7.2-20.0 versus 5.4-13.0). No significant differences in concentrations of serum T3 and TSH.</td>
<td>Michael et al. 1996</td>
</tr>
<tr>
<td>South Africa, 671 children, ages 6, 12, and 15, from six towns selected by fluoride concentration of drinking water</td>
<td>Low: 0.3 and 0.5 mg/L Medium: 0.9 and 1.1 mg/L High: 1.7 and 2.6 mg/L</td>
<td>Iodine in water, 105 to &gt; 201 µg/L(^d) Iodine in urine, 193 to &gt; 201 µg/L(^d) (median values) Iodine status considered sufficient (possibly even high)</td>
<td>Goiter prevalence ranged from 5.2% to 29.0% (15.3-29.0% for 5 of the 6 towns). The two towns with the highest fluoride had the highest goiter rates (27.7 and 29.0%). The town with 5.2% goiter prevalence had substantially less undernutrition than the other 5 towns.</td>
<td>Jooste et al. 1999</td>
</tr>
</tbody>
</table>

\(^a\) Fluoride concentration and exposure duration/conditions.

\(^d\) Median values.
India, 90 children, ages 7-18 with enamel fluorosis; 21 controls, ages 8-20 without enamel fluorosis
Case-control study, subjects with and without enamel fluorosis, also selected by water fluoride concentration; cross-sectional; ecologic exposure measure (water fluoride concentration) but urine and serum fluoride also measured
Children with dental fluorosis: 1.1-14.3 mg/L (mean, 4.37 mg/L)
Children without fluorosis: Group I, 0.14-0.81 mg/L (mean, 0.23 mg/L); Group II, 0.14-0.73 mg/L (mean, 0.41 mg/L)
Lifelong

Iodine supplementation via iodized salt for more than a decade previously, considered satisfactory
49 of 90 children with fluorosis had “well-defined hormonal derangements”; findings were borderline in the remaining 41 children.
Five distinct categories of hormonal deviations:
- normal FT4 and FT3, elevated TSH (subclinical hypothyroidism, 23 of 90)
- normal FT4 and TSH, low FT3 (low T3 syndrome, 16 of 90); borderline low T3 in many of the other children
- normal FT4, elevated FT3 and TSH (7 of 90); T4 on low end of normal range, possible T3 toxicosis
- normal FT3, low FT4, elevated TSH (2 of 90)
- normal FT4, low FT3, elevated TSH (1 of 90)

Categories 2-5 all associated with or can be caused by abnormal deiodinase activity.
Only 4 control children had serum fluoride concentrations below the normal upper limit; approximately 50% of the control children also had “hormonal deviations”; children with “safe” water (< 1 mg/L fluoride) were taking in too much fluoride, presumably from nonwater sources.

Susheela et al. 2005

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<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Fluoride Concentration(^a) and Exposure Duration/Conditions</th>
<th>Iodine Status and Other Information</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary fluoride concentrations (normal upper limit, 0.1 mg/L):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Children with fluorosis, 0.41-12.8 mg/L (mean, 3.96 mg/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls, 0.09-4.2 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum fluoride concentrations (normal upper limit, 0.02 mg/L):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Children with fluorosis, 0.02-0.41 mg/L (mean, 0.14 mg/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls, 0.02-0.29 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Due to the great range of ages included in the various studies, and because the reports do not include dose estimates (mg/kg/day), comparisons in this table are best made in terms of fluoride concentrations in drinking water. Approximations of representative doses have been made as follows: Day and Powell Jackson (1972) (iodine deficiency present): \([F] \geq 0.2 \text{ mg/L}; \text{ intake of 1 L/day for a 20-kg child}; \text{ approximate dose } \geq 0.01 \text{ mg/kg/day.}\)

Bachinskii et al. (1985): \([F] = 1.6-3.5 \text{ mg/L}; \text{ intake of 2 L/day for a 70-kg adult}; \text{ approximate dose, 0.05-0.1 mg/kg/day.}\)

Lin et al. (1991) (iodine deficiency present): \([F] = 0.88 \text{ mg/L}; \text{ intake of 1 L/day for a 30-kg child}; \text{ approximate dose, 0.03 mg/kg/day.}\)

Michael et al. (1996): \([F] = 1.0-6.5 \text{ mg/L}; \text{ intake of 2 L/day for a 60-kg adult}; \text{ approximate dose, 0.03-0.22 mg/kg/day.}\)

Jooste et al. (1999): \([F] = 1.7 \text{ and 2.6 mg/L}; \text{ intake of 1 L/day for a 20-kg child or 2 L/day for a 50-kg teenager}; \text{ approximate doses, 0.09-1.3 mg/kg/day for the child and 0.07-0.1 mg/kg/day for the teenager.}\)

Susaheela et al. (2005): \([F] = 1.1-14.3 \text{ mg/L}; \text{ intake of 2 L/day for a 50-kg teenager}; \text{ approximate dose, 0.04-0.6 mg/kg/day.}\)

McLaren (1976) suggested that these individuals should not have been included in the samples or else that further research on the etiology should have been carried out.

The units for serum T4 given by Michael et al. 1996 are ng/mL, but most likely µg/dL was meant. In units of ng/dL, these mean values are in the normal range for the controls and slightly above the normal range for the endemic fluorosis population. If the values are in ng/mL, then both means are below the normal range for serum T4.

Iodine concentrations reported as 0.83 to > 1.58 µmol/L in water and 1.52 to > 1.58 µmol/L in urine.

ABBREVIATIONS: FT3, free T3; FT4, free T4; PBI, protein-bound iodine.
### TABLE E-5 Summary of Selected Parameters for Six South African Towns

<table>
<thead>
<tr>
<th>Town</th>
<th>Sample Size</th>
<th>Fluoride in Drinking Water, mg/L</th>
<th>Goiter Prevalence, %</th>
<th>Median Urinary Iodine, µg/L&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Iodine in Drinking Water, µg/L&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Iodine in Iodized Salt, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williston</td>
<td>85</td>
<td>0.3</td>
<td>15.3</td>
<td>&gt; 201</td>
<td>105</td>
<td>28</td>
</tr>
<tr>
<td>Victoria West</td>
<td>127</td>
<td>0.5</td>
<td>17.3</td>
<td>&gt; 201</td>
<td>&gt; 201</td>
<td>5</td>
</tr>
<tr>
<td>Frazerburg</td>
<td>87</td>
<td>0.9</td>
<td>18.4</td>
<td>193</td>
<td>127</td>
<td>11</td>
</tr>
<tr>
<td>Carnarvon</td>
<td>95</td>
<td>1.1</td>
<td>5.2</td>
<td>&gt; 201</td>
<td>—&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9</td>
</tr>
<tr>
<td>Brandvlei</td>
<td>94</td>
<td>1.7</td>
<td>27.7</td>
<td>&gt; 201</td>
<td>&gt; 201</td>
<td>5</td>
</tr>
<tr>
<td>Kenhardt</td>
<td>183</td>
<td>2.6</td>
<td>29.0</td>
<td>&gt; 201</td>
<td>143</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reported as > 1.58, > 1.58, 1.52, > 1.58, > 1.58, and > 1.58 µmol/L, respectively.

<sup>b</sup>Reported as 0.83, > 1.58, 1.00, > 1.58, and 1.13 µmol/L, respectively.

<sup>c</sup>No water sample.

### TABLE E-6 Summary of Findings in Healthy Persons and Persons with Thyroid Disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Region</th>
<th>No.</th>
<th>Fluoride in Drinking Water, mg/L</th>
<th>Fluoride in Urine, mg/L</th>
<th>Fluoride in Urine, mg/day</th>
<th>Fluoride in Serum, mg/L</th>
<th>Fluoride in Erythrocytes, mg/L</th>
<th>$^{131}$I Uptake, 24 hours, %</th>
<th>T4, µg/dL$^a$</th>
<th>T3, ng/dL$^b$</th>
<th>TSH, milliunits/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroid</td>
<td>I</td>
<td>21</td>
<td>1.2 ±</td>
<td>1.5 ±</td>
<td>2.1 ±</td>
<td>0.18 ±</td>
<td>0.46 ±</td>
<td>61 ±</td>
<td>19 ±</td>
<td>340 ±</td>
<td>8 ±</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>22</td>
<td>2.2 ±</td>
<td>2.9 ±</td>
<td>3.9 ±</td>
<td>0.19 ±</td>
<td>0.51 ±</td>
<td>72 ±</td>
<td>20 ±</td>
<td>460 ±</td>
<td>0.6 ±</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>I</td>
<td>14</td>
<td>1.1 ±</td>
<td>1.4 ±</td>
<td>1.6 ±</td>
<td>0.23 ±</td>
<td>0.55 ±</td>
<td>8.5 ±</td>
<td>2.0 ±</td>
<td>72 ±</td>
<td>51 ±</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>19</td>
<td>2.5 ±</td>
<td>2.8 ±</td>
<td>3.7 ±</td>
<td>0.29 ±</td>
<td>0.61 ±</td>
<td>9.8 ±</td>
<td>2.3 ±</td>
<td>65 ±</td>
<td>58 ±</td>
</tr>
<tr>
<td>Controls</td>
<td>I</td>
<td>17</td>
<td>1.0 ±</td>
<td>1.5 ±</td>
<td>1.9 ±</td>
<td>0.21 ±</td>
<td>0.55 ±</td>
<td>24 ±</td>
<td>7.5 ±</td>
<td>180 ±</td>
<td>2.4 ±</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>30</td>
<td>2.3 ±</td>
<td>2.4 ±</td>
<td>2.7 ±</td>
<td>0.25 ±</td>
<td>0.61 ±</td>
<td>33 ±</td>
<td>7.3 ±</td>
<td>130 ±</td>
<td>4.3 ±</td>
</tr>
</tbody>
</table>

$^a$Reported as 250 ± 16, 261 ± 23, 26 ± 7, 29 ± 2, 97 ± 8, and 94 ± 6 nmol/L, respectively.

$^b$Reported as 5.2 ± 0.7, 7.1 ± 1.8, 1.1 ± 0.4, 1.0 ± 0.1, 2.8 ± 0.3, and 2.0 ± 0.2 nmol/L, respectively.

$^c$P < 0.05 compared with controls residing in Region I.

$^d$P < 0.05 compared with patients with corresponding thyropathies residing in Region I.

$^e$P < 0.05 compared with controls residing in Region II.

SOURCE: Adapted from Bachinskii et al. (1985).
<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Exposure Conditions and Duration</th>
<th>Fluoride Concentration or Dose</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland, patients with hyperthyroidism, males and females, 15 total Clinical trial; nonblinded; comparison with before-treatment values; mechanistic rather than therapeutic study</td>
<td>NaF, orally (3 times per day) or intravenously (once per day) Iodine status not given 20-245 days</td>
<td>2-10 mg/day [0.029-0.14 mg/kg/day]$^a$</td>
<td>Clinical improvement in 6 of 15 patients (symptoms of hyperthyroidism relieved, both BMR and plasma PBI reduced to normal concentrations); BMR or PBI was often improved in the other 9 Greatest improvement in women between 40 and 60 years old with a moderate degree of thyrotoxicosis.</td>
<td>Galletti and Joyet 1958</td>
</tr>
<tr>
<td>Germany, women with osteoporosis, 26 total completed 6 months of treatment (median age 62.1 years) Clinical therapeutic trial; nonblinded; comparison with before-treatment values; 38 patients originally enrolled, 3 excluded for disturbance of thyroid function</td>
<td>NaF, orally (twice per day) Iodine status not given Only 10 patients took their medicine regularly (as indicated by measurements of plasma fluoride) 6 months</td>
<td>36 mg/day or less Reduction to half dose necessary for 6 patients [0.3 or 0.6 mg/kg/day]$^b$</td>
<td>Tested for T3 uptake, T4, free T4 index, T3, and TSH; tested before start of trial and after 3 and 6 months. No changes observed in thyroid function or size.</td>
<td>Eichner et al. 1981</td>
</tr>
<tr>
<td>Study Population(s) and Type</td>
<td>Exposure Conditions and Duration</td>
<td>Fluoride Concentration or Dose</td>
<td>Effects</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>-------------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Denmark, osteoporosis patients, 140 females, 23 males, aged 16-84 years, mean 63.7 years Clinical therapeutic trial; non-blinded; 163 consecutive patients (1975-1983) presenting with osteoporosis and at least one atraumatic spinal fracture and who started treatment with fluoride, calcium and vitamin D; comparison with before-treatment values</td>
<td>NaF, orally (3 times per day with meals) Iodine status not given Calcium phosphate and vitamin D were supplemented Mean duration 2.8 years (5 years for 43 patients)</td>
<td>27 mg/day during first year Later adjusted to maintain serum fluoride between 0.095 and 0.19 mg/L (5 and 10 µmol/L) [0.45 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No changes in thyroid function (T4, T3, T3 uptake, TSH). Joint-related (51%) and gastrointestinal (25%) side effects at some point during treatment; 6% withdrew due to side effects; side effects rare when doses reduced to 14-18 mg/day.</td>
<td>Hasling et al. 1987</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on 70-kg body weight.
<sup>b</sup>Based on 60-kg body weight.

ABBREVIATIONS: BMR, basal metabolic rate; PBI, protein-bound iodine
TABLE E-8 Effects of Fluoride on Thyroid Parafollicular Cell Function in Experimental Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (Sprague-Dawley, albino, 200 g at start, 16 total, both sexes)</td>
<td>A: Drinking water (8 animals)</td>
<td>A: 40 mg/L [4 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>A: 2 months</td>
<td>No morphological differences in parafollicular cells.</td>
<td>Sundström 1971</td>
</tr>
<tr>
<td></td>
<td>B: Intraperitoneal (4 animals)</td>
<td>B: 20 mg/kg/day</td>
<td>B: 4 days (lived with controls for 2 months, ip injections on last 4 days)</td>
<td>No evidence for short-term release of calcitonin, but calcitonin not directly measured.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: Controls (4 animals)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigs (females, 20 with thyroidectomy at 10 weeks old, 20 intact; 8 months old at start of experiment; bred at 8 1/2 months old)</td>
<td>Basal ration (Ca deficient); basal ration plus Ca and P; basal ration plus NaF; basal ration plus Ca, P, and NaF Iodinated casein (0.2 g/day) fed to thyroidectomized animals</td>
<td>2 mg/kg/day (fluoride in ration adjusted periodically to maintain this dose)</td>
<td>Approximately 6 months</td>
<td>Retarding effect on cortical bone remodeling; intact thyroid gland necessary for this effect (effect not seen in thyroidectomized animals with replacement of thyroid hormone but not calcitonin). Bone fluoride in intact animals (µg/g): basal, 285; basal plus Ca and P, 181; basal plus NaF, 3,495; basal plus Ca, P, and NaF, 3,249. Bone fluoride in thyroidectomized animals (ppm): basal, 280; basal plus Ca and P, 252; basal plus NaF, 3323; basal plus Ca, P, and NaF, 3197.</td>
<td>Rantanen et al. 1972</td>
</tr>
</tbody>
</table>

<sup>a</sup>Information in brackets was calculated from information given in the papers or as otherwise noted.

<sup>b</sup>Based on water consumption of about 10% of body weight.
### TABLE E-9 Effects of Fluoride on Thyroid Parafollicular Cell Function in Humans

<table>
<thead>
<tr>
<th>Study Population(s) and Type</th>
<th>Exposure Conditions and Duration</th>
<th>Concentration or Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females), mean age 29 years; 5 controls (3 males, 2 females) mean age 31 years</td>
<td>Drinking water, area with endemic skeletal fluorosis  2 persons had moved to nonendemic areas 5 or 2 years previously  Exposed since birth Symptomatic for 10-15 years</td>
<td>A) 8.7-9.2 mg/day for 3 persons (7.8-8.0 mg/L in water) [0.143-0.15 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;  B) 21.0-52.0 mg/day for 4 persons (24.5-25.0 mg/L in water) [0.35-0.87 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;  C) 2.5 and 3.8 mg/day for 2 persons (0.8 and 1.8 mg/L in water) [0.04-0.06 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;  D) 1.2-2.2 mg/day for 5 controls (0.7-1.0 mg/L in water) [0.02-0.04 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Elevated calcitonin concentrations: A, 3 of 3; B, 4 of 4; C, 1 of 2 (8 of 8 individuals with intake ≥ 3.8 mg/day; plasma fluoride ≥ 0.11 mg/L (5.7 µmol/L); urinary fluoride ≥ 2.2 mg/day).</td>
<td>Teotia et al. 1978</td>
</tr>
<tr>
<td>Russia, description of subjects not available</td>
<td>Occupational exposure (fluorine production)  Duration not available</td>
<td>Not available</td>
<td>Elevated concentrations of calcitonin in blood.</td>
<td>Tokar’ et al. 1989</td>
</tr>
<tr>
<td>Occupational study; probably cross-sectional; full details not available</td>
<td>Drinking water  Comparison of groups with adequate (&gt;800 mg/day) and inadequate (&lt;300 mg/day) dietary calcium intake  Exposed since birth</td>
<td>1.5-25 mg/L</td>
<td>Normal or elevated plasma calcitonin.</td>
<td>Teotia et al. 1998</td>
</tr>
<tr>
<td>Review of epidemiological studies from 1963-1997 (45,725 children)</td>
<td>Occupational exposure  Duration not available</td>
<td>Not available</td>
<td>Elevated concentrations of serum calcitonin and parathyroid hormone.</td>
<td>Huang et al. 2002</td>
</tr>
</tbody>
</table>

See also Tables E-4, E-10, and E-12

<sup>a</sup>Doses in brackets were calculated from information given in the papers; other information is as reported.

<sup>b</sup>Based on 60-kg body weight.
TABLE E-10 Summary of Selected Findings for Nine Patients with Endemic Skeletal Fluorosis and Five Controls

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Fluoride in Drinking Water, mg/L</th>
<th>Fluoride Intake, mg/day</th>
<th>Urinary Fluoride, mg/day</th>
<th>Plasma Fluoride, mg/L</th>
<th>Urinary Calcium, mg/day</th>
<th>Plasma Calcium, mg/dL</th>
<th>Plasma Calcitonin, µg/L</th>
<th>IPTH, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1_control</td>
<td>35</td>
<td>F</td>
<td>1.0</td>
<td>1.2</td>
<td>0.8</td>
<td>0.023</td>
<td>120</td>
<td>9.5</td>
<td>&lt; 0.08</td>
<td>&lt; 0.35</td>
</tr>
<tr>
<td>3_control</td>
<td>22</td>
<td>M</td>
<td>0.8</td>
<td>1.6</td>
<td>0.2</td>
<td>0.021</td>
<td>115</td>
<td>10.0</td>
<td>&lt; 0.08</td>
<td>&lt; 0.40</td>
</tr>
<tr>
<td>2_control</td>
<td>25</td>
<td>M</td>
<td>0.8</td>
<td>1.8</td>
<td>0.6</td>
<td>0.030</td>
<td>95</td>
<td>10.2</td>
<td>&lt; 0.08</td>
<td>&lt; 0.50</td>
</tr>
<tr>
<td>4_control</td>
<td>32</td>
<td>M</td>
<td>0.7</td>
<td>2.0</td>
<td>1.0</td>
<td>0.020</td>
<td>170</td>
<td>9.6</td>
<td>&lt; 0.08</td>
<td>&lt; 0.35</td>
</tr>
<tr>
<td>5_control</td>
<td>34</td>
<td>F</td>
<td>1.0</td>
<td>2.2</td>
<td>1.2</td>
<td>0.038</td>
<td>130</td>
<td>9.8</td>
<td>&lt; 0.08</td>
<td>&lt; 0.35</td>
</tr>
<tr>
<td>2*</td>
<td>25</td>
<td>M</td>
<td>0.8</td>
<td>2.5 (38)*</td>
<td>1.2</td>
<td>0.036</td>
<td>85</td>
<td>10.1</td>
<td>&lt; 0.08</td>
<td>&lt; 0.55</td>
</tr>
<tr>
<td>4*</td>
<td>18</td>
<td>M</td>
<td>1.8</td>
<td>3.8 (30)*</td>
<td>2.2</td>
<td>0.12</td>
<td>80</td>
<td>9.7</td>
<td>0.14*</td>
<td>0.40</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>M</td>
<td>7.8</td>
<td>8.7</td>
<td>3.2</td>
<td>0.15</td>
<td>65</td>
<td>8.9</td>
<td>0.10*</td>
<td>0.70*</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>8.0</td>
<td>9.2</td>
<td>4.2</td>
<td>0.15</td>
<td>60</td>
<td>8.3</td>
<td>0.10*</td>
<td>0.50</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>M</td>
<td>8.0</td>
<td>9.2</td>
<td>5.8</td>
<td>0.18</td>
<td>70</td>
<td>8.8</td>
<td>0.12*</td>
<td>0.35</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>24.5</td>
<td>21.0</td>
<td>10.0</td>
<td>0.11</td>
<td>75</td>
<td>9.8</td>
<td>0.18*</td>
<td>0.40</td>
</tr>
<tr>
<td>3*</td>
<td>34</td>
<td>F</td>
<td>25.0</td>
<td>28.0</td>
<td>11.0</td>
<td>0.17</td>
<td>70</td>
<td>9.65</td>
<td>0.18*</td>
<td>1.10*</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>M</td>
<td>25.0</td>
<td>48.0</td>
<td>15.0</td>
<td>0.14</td>
<td>65</td>
<td>9.8</td>
<td>0.10*</td>
<td>0.80*</td>
</tr>
<tr>
<td>9*</td>
<td>58</td>
<td>M</td>
<td>25.0</td>
<td>52.0</td>
<td>18.5</td>
<td>0.26</td>
<td>78</td>
<td>10.6</td>
<td>0.10*</td>
<td>1.50*</td>
</tr>
</tbody>
</table>

aCase number as reported by Teotia et al. (1978), arranged in order of increasing fluoride intake. Control subjects are indicated. Asterisks by the case numbers indicate patients no longer living in the high-fluoride area; case 2 had moved 5 years previously and case 4 had moved 2 years previously.

bPlasma fluoride reported in µmol/L as follows: 1.2, 1.12, 1.6, 1.05, 2.0, 1.9, 6.1, 7.8, 8.0, 9.7, 5.7, 9.2, 7.5, and 13.6.

cPlasma immunoreactive parathyroid hormone.
dFluoride intake before moving had been 38 mg/day.
eFluoride intake before moving had been 30 mg/day.
fConsidered elevated above calcitonin concentrations found in normal controls.
gListed as “<0.10” in Table 1 of Teotia et al. (1978) but assumed to be a misprint of “0.10” based on information in the text of that paper.
hConsidered elevated above IPTH concentrations found in normal controls.
iPatient had radiographic findings suggestive of secondary hyperparathyroidism.

SOURCE: Adapted from Teotia et al. (1978).
<table>
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<tr>
<th>Species and Strain</th>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep (4 pairs of twin lambs)</td>
<td>Drinking water No information on dietary calcium</td>
<td>200 mg/L (NaF) [90 mg/L] [9 mg/kg/day]$^a$</td>
<td>1 week or 1 month</td>
<td>After 1 week, only slight changes in parathyroid ultrastructure; after 1 month, hypertrophy and ultrastructural changes considered to be indicative of increased activity in most cells. Fivefold increase in blood PTH as early as 1 week, remained raised through 1 month. Severely reduced skeletal growth, no evidence of increased resorption, no definite pathology of kidney.</td>
<td>Faccini and Care 1965</td>
</tr>
<tr>
<td>Rabbits (strain and sex not stated, 48-42 days old at start)</td>
<td>Oral supplement No information on dietary calcium</td>
<td>10 mg/kg/day</td>
<td>14 weeks; some animals followed for another 24 weeks after withdrawal of fluoride</td>
<td>No significant differences in serum calcium or magnesium; no significant differences in histological, morphometric, or ultrastructural features; no evidence for increased production of PTH or secondary hyperparathyroidism. PTH concentrations not measured.</td>
<td>Rosenquist and Boquist 1973</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, weanling male, 45 g; either thyroid-parathyroidectomized or sham-operated; 17-21 animals per group)</td>
<td>Drinking water 0.6 % calcium in diet</td>
<td>90 mg/L [9 mg/kg/day]$^b$ Controls, &lt;1 mg/L</td>
<td>15 days</td>
<td>No effect of fluoride on serum calcium, serum phosphorus, or body weight in either group. No effect of fluoride on serum immunoreactive PTH in sham-operated group. Significantly increased periosteal bone formation, significantly decreased endosteal bone formation, increased endosteal bone resorption; effects on bone were thought not to be due to increased PTH activity.</td>
<td>Liu and Baylink 1977</td>
</tr>
</tbody>
</table>
**TABLE E-11**
Effects of Fluoride on Parathyroid Function in Experimental Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
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<td>Drinking water</td>
<td>200 mg/L (NaF) [90 mg/L] [9 mg/kg/day]</td>
<td>1 week or 1 month</td>
<td>Ultrastructural evidence (from transmission electron microscopy) of increased parathyroid activity; higher percentage of active chief cells (90% versus 6%), increased numbers of secretory granules, accumulation of glycogen granules. Results considered indicative of a type of secondary hyperparathyroidism. After 1 week, only slight changes in parathyroid ultrastructure; after 1 month, hypertrophy and ultrastructural changes. Severely reduced skeletal growth, no evidence of increased resorption, no definite pathology of kidney.</td>
</tr>
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<td>Rabbits (strain and sex not stated, 48-42 days old at start)</td>
<td>Oral supplement</td>
<td>10 mg/kg/day</td>
<td>14 weeks; some animals followed for another 24 weeks after withdrawal of fluoride</td>
<td>No significant differences in serum calcium or magnesium; no significant differences in histological, morphometric, or biochemical features; no evidence for increased production of PTH or secondary hyperparathyroidism. PTH concentrations not measured.</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, weanling male, 45 g; either thyroid-parathyroidectomized or sham-operated; 17-21 animals per group)</td>
<td>Drinking water</td>
<td>90 mg/L [9 mg/kg/day]</td>
<td>15 days</td>
<td>No effect of fluoride on serum calcium, serum phosphorus, or body weight in either group. No effect of fluoride on bone volume, bone ultrastructure; effects on bone were thought not to be due to increased PTH activity.</td>
</tr>
<tr>
<td>Rats (Wistar albino, males, 95-105 g; 5 animals per group)</td>
<td>Intraperitoneal</td>
<td>15.8 mg/kg (35 mg/kg NaF)</td>
<td>Single dose, killed 0-24 hours later</td>
<td>Increased serum phosphorus; decreased urinary phosphorus; no change in serum calcium; increased urinary calcium; increased calcium, magnesium, and cAMP in renal cells (increase in cAMP was temporary); increased activity of Ca(^{2+})-ATPase in kidney. Effects were suppressed in thyroid-parathyroidectomized animals. PTH concentrations not measured.</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, males, 290-300 g; 12 animals per group)</td>
<td>Drinking water</td>
<td>150 mg/L [15 mg/kg/day]</td>
<td>10 weeks</td>
<td>Ultrastructural evidence (from transmission electron microscopy) of increased parathyroid activity; higher percentage of active chief cells (90% versus 6%), increased numbers of secretory granules, accumulation of glycogen granules. Results considered indicative of a type of secondary hyperparathyroidism. After 1 week, only slight changes in parathyroid ultrastructure; after 1 month, hypertrophy and ultrastructural changes. Severely reduced skeletal growth, no evidence of increased resorption, no definite pathology of kidney.</td>
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<td>Increased serum phosphorus; decreased urinary phosphorus; no change in serum calcium; increased urinary calcium; increased calcium, magnesium, and cAMP in renal cells (increase in cAMP was temporary); increased activity of Ca(^{2+})-ATPase in kidney. Effects were suppressed in thyroid-parathyroidectomized animals. PTH concentrations not measured.</td>
</tr>
<tr>
<td>Rats (Wistar, male, age 5 weeks, 80 g; 40 animals total)</td>
<td>Drinking water and feed</td>
<td>50 mg/L in treated group, 0.5 mg/L in controls Feed: 5 mg/kg feed (0.26 mM/kg feed) [Approximate doses: treated group, 5.4 mg/kg/day; controls, 0.45 mg/kg/day]</td>
<td>46 weeks</td>
<td>Average serum immunoreactive PTH reduced in fluoride-treated animals (not significantly) at 35 weeks. At 51 weeks, normal increase in PTH in response to a dietary calcium deficiency did not occur in fluoride-treated animals (inhibition of normal parathyroid function). Small but significant increase in calculated cytoplasmic volume was observed in calcium-deficient animals given fluoride. Normal serum calcium concentrations in all groups.</td>
</tr>
</tbody>
</table>

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[Fluoride in Drinking Water: A Scientific Review of EPA’s Standards](http://www.nap.edu/catalog/11571.html)
<table>
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</tr>
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<tbody>
<tr>
<td>Pigs (female, 8 months old, average weight 112 kg; 8 animals per group)</td>
<td>Daily oral supplement High calcium and vitamin D in diet</td>
<td>2 mg/kg/day (Fluoride in feed and water approximately 0.05 mg/kg/day)</td>
<td>6 months (average weight, 166 kg)</td>
<td>Plasma fluoride (mg/L): controls, 0.013; treated, 0.24; peak (40-100 minutes after dose), &gt;1.9. Skeletal fluorosis without changes in plasma calcium, parathyroid activity, or vitamin D concentrations. No effect on PTH (measured after 4 months).</td>
<td>Andersen et al. 1986</td>
</tr>
<tr>
<td>Sheep (females, 3 breeds, average age 6.0 ± 2.8 years, 55-60 kg; 2 groups of 7 animals)</td>
<td>Oral with dry feed Normal dietary calcium without calcium supplementation</td>
<td>0.45 or 2.3 mg/kg/day (NaF 1 or 5 mg/kg/day)$^d$</td>
<td>45 days</td>
<td>Significant decrease in serum calcium and phosphorus in both groups; significant increase in osteocalcin in second group. Variable increase in serum PTH in both groups, not statistically significant due to wide variation, but mean serum PTH in both groups at least twice as high at 45 days (4.9 ± 3.5 and 3.9 ± 0.9 milliunits/mL) as at beginning of experiment (1.9 ± 0.3 milliunits/mL in both groups). Effects on osteoblast birth rate and life span; increased bone formation and resorption, but formation greater than resorption (net increase in bone mass); possible secondary hyperparathyroidism. Serum fluoride (means, mg/L): initial (both groups), 0.10-0.11; final (45 days), first group, 0.24, second group, 0.82; peak &gt; 0.5 at 3 hours after single dose of NaF at 3.5 mg/kg (fluoride, 1.6 mg/kg). Bone fluoride (means, ppm in ash): initial, 2,200-2,500; final, 2,700-3,200.</td>
<td>Chavassieux et al. 1991</td>
</tr>
</tbody>
</table>

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$^a$ Exposure duration varies by study. $^b$ Bone density and bone metabolism at end of experiment. $^c$ Bone mineral density at end of experiment. $^d$ Oral with dry feed Normal dietary calcium without calcium supplementation.
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<td>High calcium and vitamin D in diet</td>
<td>2 mg/kg/day (Fluoride in feed and water approximately 0.05 mg/kg/day)</td>
<td>6 months (average weight, 166 kg)</td>
<td>Plasma fluoride (mg/L): controls, 0.013; treated, 0.24; peak (40-100 minutes after dose), &gt;1.9. Skeletal fluorosis without changes in plasma calcium, parathyroid activity, or vitamin D concentrations. No effect on PTH (measured after 4 months).</td>
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<td>Normal dietary calcium without calcium supplementation</td>
<td>0.45 or 2.3 mg/kg/day (NaF 1 or 5 mg/kg/day)</td>
<td>45 days</td>
<td>Significant decrease in serum calcium and phosphorus in both groups; significant increase in osteocalcin in both groups. Decreased serum fluoride at 3.5 mg/kg (fluoride) and 3.5 mg/kg NaF at 3.5 mg/kg (fluoride, 1.6 mg/kg). Bone fluoride (means, ppm in ash): initial, 2,200-2,500; final, 2,700-3,200.</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, male, 40-50 g weanlings at start, 68-77 animals per group)</td>
<td>Drinking water</td>
<td>5, 15, or 50 mg/L (0.26-0.45, 0.69-1.31, and 2.08-3.46 mg/kg/day, decreasing with increasing body weight)</td>
<td>3, 6, 12, or 18 months</td>
<td>“No significant effect” on plasma calcium or alkaline phosphatase; specific data by treatment group not reported. PTH concentrations not measured.</td>
<td>Dunipace et al. 1995</td>
</tr>
<tr>
<td>Rats (strain not available)</td>
<td>Drinking water</td>
<td>100 mg/L (0.27-0.44 mg/kg/day)</td>
<td>2 months</td>
<td>Animals on low-calcium diet: osteomalacia, osteoporosis, accelerated bone turnover, increased serum alkaline phosphatase, increased osteocalcin, increased PTH.</td>
<td>Li and Ren 1997</td>
</tr>
<tr>
<td>Rats (strain not available)</td>
<td>Drinking water</td>
<td>Dietary calcium adequate or low</td>
<td>100 mg/L (10 mg/kg/day)</td>
<td>Animals on adequate calcium diet: slightly increased osteoblastic activity (elevated serum alkaline phosphatase activity and increased average width of trabecular bone after 1 year).</td>
<td>continued</td>
</tr>
<tr>
<td>Species and Strain</td>
<td>Exposure Conditions</td>
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<tr>
<td>--------------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, male, 30 to 40 g weanlings at start, 432 animals total)</td>
<td>Drinking water Either calcium-deficient diet or diet deficient in protein, energy, or total nutrients</td>
<td>5, 15, or 50 mg/L ([0.5, 1.5, \text{or } 5 \text{ mg/kg/day}]^b)</td>
<td>16 or 48 weeks</td>
<td>No significant effect on plasma calcium or alkaline phosphatase; specific data by fluoride treatment group not reported. Calcium-deficient animals absorbed and retained more fluoride than controls and, in highest fluoride group, gained significantly less weight. Combination of general malnutrition and calcium deficiency was not examined.</td>
<td>Dunipace et al. 1998</td>
</tr>
<tr>
<td>Monkeys (cynomolgus, females, 2.5-3.5 kg)</td>
<td>Isoflurane anesthesia</td>
<td>Not available</td>
<td>2 hours</td>
<td>Increased serum inorganic fluoride; decreased ionized calcium; increased PTH and osteocalcin in response to decreased calcium. Serum fluoride 0.070 mg/L versus 0.046 mg/L with ketamine/atropine anesthesia.</td>
<td>Hotchkiss et al. 1998</td>
</tr>
<tr>
<td>Rats (Wistar, females, 4-5 months old, 130-150 g)</td>
<td>Drinking water</td>
<td>500 mg/L ((50 \text{ mg/kg/day})^{b/f})</td>
<td>60 days</td>
<td>Hypocalcemia, attributed to suppressed gastrointestinal absorption of calcium. Decreased weight gain; inhibition of acetylcholinesterase and total cholinesterase in brain and serum; decreased spontaneous motor activity and endurance time. PTH not measured.</td>
<td>Ekambaram and Paul 2001</td>
</tr>
<tr>
<td>Rats (Wistar, adult females, 150-170 g at start; fluoride administered during pregnancy and lactation)(^g)</td>
<td>NaF orally by feeding tube</td>
<td>40 mg/kg/day NaF ((18 \text{ mg/kg/day fluoride to the mothers}))</td>
<td>Day 6 of gestation through day 21 of lactation</td>
<td>Hypocalcemia in mothers and offspring. PTH not measured. Significant changes in other serum cations (sodium, potassium) and phosphorus. Significant recovery on withdrawal of NaF.</td>
<td>Verma and Guna Sherlin 2002b</td>
</tr>
</tbody>
</table>

\(^a\) Information in brackets was calculated from information given in the papers or as otherwise noted.

\(^b\) Based on water consumption of about 10% of body weight.

\(^c\) Based on water consumption of about 10% of body weight and feed consumption of about 8% of body weight; ATSDR (2003) gives a fluoride dose of 3.3 mg/kg (presumably per day) for these animals.

\(^d\) Choice of doses based on a therapeutic dose of NaF (1 mg/kg/day) and a toxic dose of fluoride (5 mg/kg/day) (Chavassieux et al. 1991).

\(^e\) Based on average daily water consumption of 163 mL, mean initial weight of 1.55 kg, and mean final weight of 2.33 kg for the fluoride-treated group.

\(^f\) The dose was selected to produce toxic effects in a short time, without lethality (Ekambaram and Paul 2001).

\(^g\) In many mammalian species, maternal fluoride exposures are not well reflected by fluoride concentrations in milk; therefore, the impacts of fetal exposure and of reduced milk production by the mothers must also be considered.
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<tr>
<td>Rats (Sprague Dawley weanlings)</td>
<td>Drinking water to dams and then to weanling pups; Some groups with calcium deficient diet (dams and pups)</td>
<td>50 mg/L (5 mg/kg/day)</td>
<td>Day 11 of gestation through 9 weeks old; continued until 15 weeks old with restored calcium, low fluoride, or both</td>
<td>Decreased serum calcium, increased serum alkaline phosphatase, increased concentrations of vitamin D metabolites (both 25(OH)D₃ and 1,25(OH)₂D₃). Decreased transcription of genes for vitamin D receptor and calbindin D 9 k; increased transcription of calcium-sensing receptor gene. Continued fluoride excess even with calcium supplementation continued to be detrimental. PTH not measured.</td>
<td>Tiwari et al. 2004</td>
</tr>
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<td>Monkeys (cynomolgus, females, 2.5-3.5 kg)</td>
<td>Isoflurane anesthesia</td>
<td>Not available 2 hours</td>
<td>Increased serum inorganic fluoride; decreased ionized calcium; increased PTH and osteocalcin in response to decreased calcium. Serum fluoride 0.070 mg/L versus 0.046 mg/L with ketamine/atropine anesthesia.</td>
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<td>Drinking water</td>
<td>500 mg/L (50 mg/kg/day)</td>
<td>60 days</td>
<td>Hypocalcemia, attributed to suppressed gastrointestinal absorption of calcium. Decreased weight gain; inhibition of intestinal absorption of calcium, decreased concentration and transaminase activity of various enzymes. Continued fluoride excess even with calcium supplementation continued to be detrimental. PTH not measured.</td>
<td>Ekambaram and Paul 2001</td>
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<td>Rats (Wistar, adult females, 150-170 g at start; fluoride administered during pregnancy and lactation)</td>
<td>NaF orally by feeding tube</td>
<td>40 mg/kg/day NaF (18 mg/kg/day fluoride to the mothers)</td>
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*g* In many mammalian species, maternal fluoride exposures are not well reflected by fluoride concentrations in milk; therefore, the impacts of fetal exposure and of reduced milk production by the mothers must also be considered.
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<th>Study Population(s) and Type</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose&lt;sup&gt;a&lt;/sup&gt; and Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark, 14 normal subjects (5 fasting, 9 nonfasting, ages 22-38 years) Experimental study</td>
<td>Oral dose of NaF</td>
<td>27 mg of fluoride (60 mg NaF) [0.4 mg/kg]&lt;sup&gt;b&lt;/sup&gt; Single dose Measurements made at 1, 2, 3, and 24 hours</td>
<td>Decreased serum calcium and phosphorus; increased immunoreactive PTH. Measured serum fluoride peak 0.8-0.9 mg/L. Variations in phosphorus clearance suggestive of a transitory hypersecretion of PTH; initial fall in serum calcium, return to preoperative concentration after 24 hours (variations in calcium balance were not highly significant). PTH not measured. Maximum serum inorganic fluoride: 0.12 mg/L (versus 0.039 mg/L in controls).</td>
<td>Larsen et al. 1978</td>
</tr>
<tr>
<td>France, 21 surgery patients (12 males and 9 females; ages 20-60 years) Experimental study; subjects had orthopedic (16), ophthalmologic (3), or plastic (2) surgery; study excluded patients who were obese, had altered renal function or previously recognized diseases, or received blood transfusions or undescibed medications; initial values used as controls</td>
<td>Enflurane anesthesia</td>
<td>Not available 60-165 min. (mean, 95.5 ± 26 minutes)</td>
<td>Variations in phosphorus clearance suggestive of a transitory hypersecretion of PTH; initial fall in serum calcium, return to preoperative concentration after 24 hours (variations in calcium balance were not highly significant). PTH not measured. Maximum serum inorganic fluoride: 0.12 mg/L (versus 0.039 mg/L in controls).</td>
<td>Duchassaing et al. 1982</td>
</tr>
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<td>Concentration or Dose</td>
<td>Effects Reference</td>
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<tr>
<td>Denmark, 14 normal subjects (5 fasting, 9 nonfasting, ages 22-38 years) Experimental study</td>
<td>Oral dose of NaF</td>
<td>27 mg of fluoride (60 mg NaF) [0.4 mg/kg]</td>
<td>Decreased serum calcium and phosphorus; increased immunoreactive PTH. Measured serum fluoride peak 0.8-0.9 mg/L. No significant increase in calcium or phosphorus clearance between fasting and nonfasting subjects except for a higher increase in serum fluoride concentration in fasting subjects. Larsen et al. 1978</td>
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<tr>
<td>France, 21 surgery patients (12 males and 9 females; ages 20-60 years) Experimental study; subjects had orthopedic (16), vascular (5), or urologic (10) recognized diseases, or received blood transfusions or undescribed medications; initial values used as controls</td>
<td>Enflurane anesthesia</td>
<td>Not available</td>
<td>Variations in phosphorus clearance suggestive of a transitory hypersecretion of PTH; initial fall in serum calcium, phosphorus, and total and ionized calcium. Some initial increase in serum alkaline phosphatase. Maximum serum inorganic fluoride: 0.12 mg/L (versus 0.039 mg/L in controls). Duchassaing et al. 1982</td>
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<tr>
<td>The Netherlands, 91 osteoporosis patients (61 females, 30 males; mean ages by type of treatment were 57.6-67.3 years) Clinical therapeutic trial; non-blinded; subjects had osteoporosis with one or more vertebral fractures before participation in the study, had normal concentrations for serum creatinine and liver enzymes, were treated as outpatients, were mobile and advised to exercise; pretreatment values used as controls</td>
<td>Oral sodium fluoride (capsules, enteric coated tablets, or enteric coated, slow release tablets) Calcium supplementation of 1,000 mg/day</td>
<td>Mean fluoride dosages by group between 18 and 36 mg/day (NaF, 40-80 mg/day) [fluoride, 0.57-1.1 mg/kg/day] 2 years</td>
<td>Patients divided into “responders” and “nonresponders” (NR) by (1) degree of increase in serum alkaline phosphatase concentration (20% NR); (2) changes in bone mineral content (26% NR); (3) occurrence of femoral neck fracture (6.6% NR). Patients with a fracture had lower serum alkaline phosphatase changes and higher increases in PTH. Duursma et al. 1987</td>
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<tr>
<td>England (7 healthy males; ages 24-43 years) Experimental study</td>
<td>Oral NaF tablets Calcium intakes 400-800 mg/day</td>
<td>27 mg/day (NaF, 60 mg/day) [fluoride, 0.39 mg/kg/day] 3 weeks, followed up 6 weeks later</td>
<td>No significant changes in plasma alkaline phosphatase, 25-hydroxy vitamin D, PTH, total and ionized calcium, phosphorus, or albumin. Significant increase in serum osteocalcin. PTH elevated slightly but not significantly (50 ± 17.6 pM/L after versus 43 ± 5.3 pM/L before); large standard deviation indicates variable response (not seen with other parameters). Dandona et al. 1988</td>
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<tr>
<td>Study Population(s) and Type</td>
<td>Exposure Conditions</td>
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<td>England, osteoporosis patients (34 females aged 49-74 years; 7 males aged 45-69 years; all with postmenopausal or idiopathic osteoporosis; all had normal renal function; 6 females were on hormone replacement therapy) Experimental study</td>
<td>NaF orally in gelatin capsules Calcium supplementation was started at least 6 weeks (median, 20 weeks) prior to study</td>
<td>27 mg/day (NaF, 60 mg/day) [fluoride, 0.39 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt; 8 days</td>
<td>Decreased serum calcium (total and ionized); decreased serum phosphorus; increased concentrations of biologically active PTH (more than 5-fold); major changes occurred within 48 hours, some return toward normal after that. Patients divided into 2 groups by stability of serum calcium and phosphorus concentrations; the groups varied in their response to NaF with respect to mineral absorption and balance.</td>
<td>Stamp et al. 1988</td>
</tr>
<tr>
<td>England, osteoporosis patients (22 controls; 2 males and 20 females, mean age 67 ± 8 years, range 51-83 years; 18 treated patients, 5 males and 13 females, mean age 61 ± 12 years, range 41-78 years; 10 patients were common to both groups [before and after treatment]; 8 females were on hormone replacement therapy) Experimental study; longitudinal for 10 patients</td>
<td>NaF orally in gelatin capsules Calcium supplementation was started prior to study</td>
<td>27 mg/day (NaF, 60 mg/day) [fluoride, 0.39 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt; 15 ± 10 months</td>
<td>Increased concentrations of biologically active PTH (bio-PTH) in treated group (log-transformed means, 10.6 versus 2.5 pg/mL; ranges, 1.6-126 versus 0.25-10.9 pg/mL). Significantly higher serum alkaline phosphatase (SAP) in treated group. Fluoride-treated patients with elevated concentrations of bio-PTH (&gt; 18 pg/mL) had significantly lower concentrations of SAP than other treated patients, indistinguishable from controls; elevated bio-PTH also associated with relative hypophosphatemia and relative hypocalciuria; possibly excessive PTH accounts for “refractory” state of some patients—nonresponsiveness to fluoride therapy.</td>
<td>Stamp et al. 1990</td>
</tr>
</tbody>
</table>
U.S., female osteoporosis patients (patients with previous history of hyperparathyroidism and several other conditions were excluded) Initial recruitment included 203 in-state patients from previous fluoride trials and 95 controls who had not taken fluoride; of these, 40 fluoride patients and 43 controls were scheduled for appointments; 15 fluoride patients were no longer taking fluoride or failed the appointments; 5 controls failed the appointments; final study included 25 fluoride patients and 38 controls (mean ages, 70.1 for fluoride group, 69.5 for controls) Cross-sectional study; fluoride-treated patients and non-treated controls recruited from database of osteoporosis patients of one investigator; fasting samples; analyses of drinking water, blood, and urine performed blindly; results reported as means of groups and as number outside the normal range for the parameter; urine and plasma fluoride were clearly different between groups; no significant difference in mean water fluoride concentrations See also Table E-17

Slow-release sodium monofluorophosphate plus calcium carbonate at 1,500 mg/day Most controls (n = 38) had calcium supplementation

23 mg/day (mean dose) [fluoride, 0.33 mg/kg/day]b
1.4-12.6 years (mean, 4.2 years)

No significant difference in mean calcium concentrations between groups; 2 of 25 individuals outside normal range (versus 0 of 38 controls).

Significant difference (elevation) in mean alkaline phosphatase concentrations between groups; 8 of 25 individuals outside normal range (versus 0 of 38 controls); for those 8, a significant elevation in bone isoenzymes was found.

For 24 of the 25 patients, calcium was significantly lower than baseline (pretreatment) values and alkaline phosphatase was significantly higher. PTH not measured.

Urine fluoride (mg/L, mean and SD): fluoride group, 9.7 (4.1); controls, 0.8 (0.5); plasma fluoride (mg/L, mean and SD)c: fluoride group, 0.17 (0.068); controls, 0.019 (0.0076)

Jackson et al. 1994

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TABLE E-12 Continued

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<tr>
<th>Study Population(s) and Type</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose$^a$ and Exposure Duration</th>
<th>Effects</th>
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<td>China, healthy adults (approximately 120 per group, with either normal or inadequate nutritional intakes; mean ages of groups, 44.9-47.7 years) Cross-sectional cohort study; subjects grouped by location (water fluoride concentration) and nutritional status; populations generally similar (e.g., socially and economically); estimated fluoride intakes and measurements of urine and plasma fluoride and other parameters were made for individuals but results reported only for groups; probable overlap between low (≤0.3 mg/L) and middle (around 1 mg/L) fluoride exposure groups for each nutritional category; no mention of whether analyses were performed blindly See also Table E-17</td>
<td>Drinking water Normal nutrition defined as &gt;75 g of protein and &gt;600 mg of Ca per day Inadequate nutrition defined as ≤60 g of protein and ≤400 mg of Ca per day</td>
<td>0.23, 1.02, and 5.03 mg/L (normal nutrition) 0.11, 0.90, and 4.75 mg/L (inadequate nutrition) Estimated intake: 1.70, 3.49, and 14.8 mg/day (normal nutrition); 1.20, 2.64, 15.32 mg/day (inadequate nutrition) At least 35 years of continuous residency in the study area</td>
<td>Significant decrease in plasma calcium concentration associated with an increase in fluoride exposure in the populations with inadequate nutrition; not detected in subjects with normal nutrition. Elevated alkaline phosphatase activity with increased fluoride exposure in all populations, with higher values in subjects with inadequate nutrition. All values$^d$ within the normal range regardless of fluoride exposure and nutritional condition. PTH concentrations not measured.</td>
<td>Li et al. 1995</td>
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</table>
U.S., osteoporosis patients
(Group I, “good responders,” 13
postmenopausal females and 3 males;
Group II, “poor responders,” 7
postmenopausal females and 3 males;
Group III, untreated controls, 10 age-
matched postmenopausal females)
Cross-sectional study of fluoride-
treated osteoporosis patients; non-
fluoride-treated osteoporosis patients
as controls

Patients who showed a rapid increase in
spinal bone density also showed a general
state of calcium deficiency and secondary
hyperparathyroidism.
Serum PTH elevated in 4 “good responders”
and 1 “poor responder” but no controls; all
5 with elevated PTH were calcium deficient;
mean PTH concentrations were similar for all
3 groups.
Degree of calcium deficiency in fluoride-
treated patients was proportional to serum
concentrations of PTH, alkaline phosphatase,
procollagen peptide, and osteocalcin and to
urine hydroxyproline concentrations.
Fluoride therapy can cause calcium deficiency,
even in patients with a high calcium intake;
osteogenic response to fluoride can increase
the skeletal requirement for calcium.

Some differences in mean plasma calcium and
phosphorus concentrations among groups
were statistically significant (lower calcium at
0.2 mg/L than 1.0 or 4.0; higher phosphorus
at 4.0 mg/L than 0.2 or 1.0); no significant
differences among mean alkaline phosphatase
concentrations; all mean values were within
normal ranges.
PTH not measured.

U.S., 199 adult volunteers (mean ages
of groups, 62.3, 58.6, 57.2 years)
Ecological study; cross-sectional;
subjects grouped by location (water
fluoride concentration); subjects
not randomly selected; nonfasting
samples; urine and plasma fluoride
concentrations significantly different
for groups; study parameters
reported by groups; no information
on whether analyses were performed
blindly
See also Table E-17
### TABLE E-12 Continued

<table>
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<tr>
<th>Study Population(s) and Type</th>
<th>Exposure Conditions</th>
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<th>Reference</th>
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<tbody>
<tr>
<td>U.S., 75 osteoporosis patients (36 with placebo and 39 with fluoride)</td>
<td>Oral doses of slow-release NaF</td>
<td>23 mg/day (NaF, 50 mg/day) [approximate fluoride dose, 0.33 mg/kg/day]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No significant changes in most parameters. Decrease in immunoreactive PTH from beginning values (due to increased calcium intake); fluoride-treated group slightly and consistently (but not significantly) higher than placebo group. Decrease in serum 1,25-dihydroxy vitamin D in placebo group but not in fluoride-treated group.</td>
<td>Zerwekh et al. 1997b</td>
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<td>Placebo-controlled therapeutic study; subjects randomly assigned to treatment groups; no information on whether analyses were performed blindly</td>
<td>Both groups given calcium at 800 mg/day as calcium citrate</td>
<td>2 cycles of 12 months of treatment, 2 months off; analyses at 0, 6, 12, and 14 months for each cycle Calcium supplemented continuously throughout</td>
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<tr>
<td>China, 50 male fluoride workers and 50 controls</td>
<td>Occupational exposure</td>
<td>Not available</td>
<td>Elevated concentrations of serum calcitonin and PTH.</td>
<td>Huang et al. 2002</td>
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<tr>
<td>Occupational cohort study; cross-sectional; measurements of fluoride in serum and urine; full details not available</td>
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<sup>a</sup>Information in brackets was calculated from information given in the papers or as otherwise noted.

<sup>b</sup>Based on 70-kg body weight.

<sup>c</sup>Reported as 9.0 (3.6) µmol/L for the fluoride group and 1.0 (0.4) µmol/L for the controls.

<sup>d</sup>Not stated whether this refers to mean values or all individual values.
<table>
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<tr>
<th>Study Population(s)</th>
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<tr>
<td>India, 25 cases of skeletal fluorosis (21 males, 4 females, aged 30-76, with radiologically proved skeletal fluorosis) 25 adult controls (19 males, 6 females, aged 25-75, not from endemic fluorosis area, and with no evidence of enamel or skeletal fluorosis or of bone or renal disease) Case-control study</td>
<td>Drinking water (endemic fluorosis areas)</td>
<td>Not given Probably lifelong</td>
<td>No significant differences between cases and controls in serum calcium, serum inorganic phosphate, phosphate clearance, or 24-hour urinary calcium excretion (the latter either on a normal diet or on days 4-6 of a low-calcium diet); mean phosphate clearance was reduced, but not significantly. Significantly higher serum alkaline phosphatase values in individuals with fluorosis. No measurements of PTH.</td>
<td>Singh et al. 1966</td>
</tr>
<tr>
<td>United States, 18-year-old boy, 57.4 kg, with renal insufficiency Case report See also Table 2-3</td>
<td>“High” intake of well water containing fluoride; current intake, 7.6 L/day (2 gallons per day)</td>
<td>2.6 mg/L [0.34 mg/kg/day] Since early childhood</td>
<td>Elevated serum immunoreactive PTH (more than 3 times normal value), slightly elevated serum calcium. Enamel fluorosis and roentgenographic bone changes consistent with “systemic fluorosis.”</td>
<td>Juncos and Donadio 1972</td>
</tr>
</tbody>
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TABLE E-13 Effects of Fluoride on Parathyroid Function in Humans (Studies of Endemic Fluorosis Patients)
<table>
<thead>
<tr>
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<tr>
<td>India, 20 patients with skeletal fluorosis (17 males, 3 females, age 42-68 years)</td>
<td>Drinking water (endemic fluorosis areas) Dietary calcium and vitamin D considered adequate</td>
<td>&gt; 25 mg/day [&gt; 0.4 mg/kg/day]&lt;sup&gt;c&lt;/sup&gt; Lifelong</td>
<td>Clear evidence of secondary hyperparathyroidism in the 5 patients studied in detail; radiological findings consistent with hyperparathyroidism. Increased plasma alkaline phosphatase, increased phosphate clearance, decreased tubular reabsorption of phosphate, increased urinary fluoride, decreased urinary calcium. Normal plasma calcium and phosphate in 4 persons; elevated plasma calcium and decreased plasma phosphate in 1 person. Elevated serum immunoreactive PTH in all 5, especially in the person with elevated plasma calcium and decreased plasma phosphate (a parathyroid adenoma was later found in that individual, possibly attributable to longstanding hyperplasia as a result of excessive fluoride intake). Excess calcium and fluoride in bone in all 5 (11.8-13.2 versus 10.8 g of calcium per 100 g of dry fat-free bone ash; 265-585 versus 30 mg of fluoride per 100 g of dry fat-free bone ash). Urinary fluoride: 3.0-4.8 mg/L/day.</td>
<td>Teotia and Teotia 1973</td>
</tr>
<tr>
<td>India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females, mean age 29 years) 5 controls (3 males, 3 females, mean age 32 years)</td>
<td>Drinking water, area with endemic skeletal fluorosis 2 persons had moved to non-endemic areas 5 or 2 years previously</td>
<td>A) 8.7-9.2 mg/day for 3 persons (7.8-8.0 mg/L in water) [0.145-0.15 mg/kg/day] B) 21.0-52.0 mg/day for 4 persons (24.5-25.0 mg/L in water) [0.35-0.87 mg/kg/day] C) 2.5 and 3.8 mg/day for 2 persons (0.8 and 1.8 mg/L in water) [0.04-0.06 mg/kg/day] D) 1.2-2.2 mg/day for 5 controls (0.7-1.0 mg/L in water) [0.02-0.04 mg/kg/day]</td>
<td>Radiographs of 2 of the 4 persons were consistent with secondary hyperparathyroidism. Increased PTH concentrations: A, 1 of 3; B, 3 of 4 [4 of 6 individuals with plasma fluoride ≥ 0.15 mg/L (7.8 µmol/L)]. Normal total and ionized calcium concentrations; normal vitamin D concentrations in children; subnormal total and ionized calcium concentrations in the mother.</td>
<td>Teotia et al. 1978</td>
</tr>
<tr>
<td>India, 4 siblings (aged 8-18; 2 males, 2 females) and their mother (age 40), all with skeletal fluorosis</td>
<td>Drinking water source, 16.2 mg/L</td>
<td>Calcium intakes considered normal (500-820 mg/day) 16-49 mg/day from water, plus any contribution from food [0.5 mg/kg/day for the younger children; 0.5-1 mg/kg/day for the older children and mother]</td>
<td>Symptomatic for at least 2 years</td>
<td>Srivastava et al. 1989</td>
</tr>
</tbody>
</table>
### Study Population(s)

| India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females; mean age 29 years) |
| 5 controls (3 males, 2 females; mean age 31 years) | Drinking water, area with endemic skeletal fluorosis |
| Case-control study; individual estimates of current fluoride intake, measurements of fasting plasma fluoride and urinary fluoride; incomplete information on selection of subjects and controls | 2 persons had moved to non-endemic areas 5 or 2 years previously |
| See also Tables E-4, E-9, and E-10 | A) 8.7-9.2 mg/day for 3 persons (7.8-8.0 mg/L in water) [0.145-0.15 mg/kg/day]\(^d\) |
| | B) 21.0-52.0 mg/day for 4 persons (24.5-25.0 mg/L in water) [0.35-0.87 mg/kg/day]\(^d\) |
| | C) 2.5 and 3.8 mg/day for 2 persons (0.8 and 1.8 mg/L in water) [0.04-0.06 mg/kg/day]\(^d\) |
| | D) 1.2-2.2 mg/day for 5 controls (0.7-1.0 mg/L in water) [0.02-0.04 mg/kg/day]\(^d\) |
| | Since birth | Normal total and ionized calcium concentrations; normal vitamin D concentrations in children; subnormal total and ionized calcium and subnormal vitamin D in the mother. Significantly elevated PTH, elevated osteocalcin, and elevated alkaline phosphatase in all 5. Findings consistent with secondary hyperparathyroidism. Skeletal changes, biochemical hyperparathyroidism, and elevated osteocalcin were similar in all 5, regardless of nutritional status (low in calories and protein for the mother, more nearly adequate for the children) and vitamin D status. Serum fluoride: 0.29-0.45 mg/L in the children (not measured in the mother). |

### India, 4 siblings (aged 8-18; 2 males, 2 females) and their mother (age 40), all with skeletal fluorosis

Drinking water source, 16.2 mg/L Calcium intakes considered normal (500-820 mg/day) 16-49 mg/day from water, plus any contribution from food [0.5 mg/kg/day for the younger children; 0.5-1 mg/kg/day for the older children and mother]\(^e\) Symptomatic for at least 2 years Increased PTH concentrations: A, 1 of 3; B, 3 of 4 [4 of 6 individuals with plasma fluoride ≥ 0.15 mg/L (7.8 µmol/L)]. Radiographs of 2 of the 4 persons were consistent with secondary hyperparathyroidism.

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\(^a\) and Exposure Duration Effects Reference

Drinking water (endemic fluorosis areas) Dietary calcium and vitamin D considered adequate

\(> 25 \text{ mg/day}\) \([> 0.4 \text{ mg/kg/day}]\)

Teotia and Teotia 1973

India, 20 patients with skeletal fluorosis (17 males, 3 females, age 42-68 years) Detailed studies on 5 of these patients ... of plasma and urine parameters and bone samples; comparison with values obtained from persons in nonfluorotic areas

Teotia et al. 1978

India, 9 patients with moderate to severe skeletal fluorosis (6 males, 3 females, mean age 29 years) 5 controls (3 males, 2 females; mean age 31 years) Case-control study; individual estimates of current fluoride intake, measurements of fasting plasma fluoride and urinary fluoride; incomplete information on selection of subjects and controls See also Tables E-4, E-9, and E-10

Drinking water, area with endemic skeletal fluorosis 2 persons had moved to non-endemic areas 5 or 2 years previously

A) 8.7-9.2 mg/day for 3 persons (7.8-8.0 mg/L in water) [0.145-0.15 mg/kg/day]\(^d\) B) 21.0-52.0 mg/day for 4 persons (24.5-25.0 mg/L in water) [0.35-0.87 mg/kg/day]\(^d\) C) 2.5 and 3.8 mg/day for 2 persons (0.8 and 1.8 mg/L in water) [0.04-0.06 mg/kg/day]\(^d\) D) 1.2-2.2 mg/day for 5 controls (0.7-1.0 mg/L in water) [0.02-0.04 mg/kg/day]\(^d\) Since birth Symptomatic for 10-15 years

Increased PTH concentrations: A, 1 of 3; B, 3 of 4 [4 of 6 individuals with plasma fluoride ≥ 0.15 mg/L (7.8 µmol/L)]. Radiographs of 2 of the 4 persons were consistent with secondary hyperparathyroidism.

Teotia et al. 1978

India, 4 siblings (aged 8-18; 2 males, 2 females) and their mother (age 40), all with skeletal fluorosis Case reports; individual estimates of fluoride intake from water, measurements of serum fluoride and other parameters; age-matched Indian controls

Drinking water source, 16.2 mg/L Calcium intakes considered normal (500-820 mg/day) 16-49 mg/day from water, plus any contribution from food [0.5 mg/kg/day for the younger children; 0.5-1 mg/kg/day for the older children and mother]\(^e\) Symptomatic for at least 2 years

Normal total and ionized calcium concentrations; normal vitamin D concentrations in children; subnormal total and ionized calcium and subnormal vitamin D in the mother. Significantly elevated PTH, elevated osteocalcin, and elevated alkaline phosphatase in all 5. Findings consistent with secondary hyperparathyroidism. Skeletal changes, biochemical hyperparathyroidism, and elevated osteocalcin were similar in all 5, regardless of nutritional status (low in calories and protein for the mother, more nearly adequate for the children) and vitamin D status. Serum fluoride: 0.29-0.45 mg/L in the children (not measured in the mother).

Srivastava et al. 1989

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<table>
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<tbody>
<tr>
<td>South Africa (260 children, 119 boys, 141 girls; ages 6-16, in an area with endemic skeletal fluorosis)</td>
<td>Drinking water</td>
<td>8-12 mg/L [0.2-1.2 mg/kg/day](^f) Probably lifelong for most For the 9 children, at least 8 years</td>
<td>Hypocalcemia present in 23% of the children; hypophosphatemia in 15%; elevated alkaline phosphatase in about 25%. Normal serum 25(OH)D concentrations in the 40 children in whom it was measured. Hypocalcemia in 6 of 9 studied individually; low concentrations of 25(OH)D in 2; elevated 1,25(OH)(_2)D in 7. Bone fluoride elevated about 10-fold in the 7 children measured: 4,430-6,790 ppm in ash, mean 5,580 ppm in ash. Reduced phosphaturic response during a PTH-stimulation test (suggestive of pseudohypoparathyroidism Type II), directly related to presence of hypocalcemia, corrected by correcting the hypocalcemia. PTH concentrations not measured. Severe hyperosteoidosis associated with secondary hyperparathyroidism and a mineralization defect. Fluoride ingestion may increase calcium requirements and exacerbate the prevalence of hypocalcemia.</td>
<td>Pettifor et al. 1989</td>
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<td>9 children (8 boys, 1 girl) studied individually; mean age, 13.7 ± 4.4 years; from the same area Prevalence (cross-sectional) study with ecologic measure of exposure; random selection of participants Case reports of 9 hospitalized individuals</td>
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<td>Pettifor et al. 1989</td>
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<td>Drinking water 8-12 mg/L [0.2-1.2 mg/kg/day]</td>
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<td>Probably lifelong for most</td>
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<td>For the 9 children, at least 8 years</td>
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<td>Hypocalcemia present in 23% of the children; hypophosphatemia in 15%; elevated alkaline phosphatase in about 25%.</td>
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<td>Normal intake of calcium is necessary for bone mineralization defect. Fluoride ingestion may increase calcium requirements and exacerbate the prevalence of hypocalcemia.</td>
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<td>Review of epidemiological studies from 1963-1997 (45,725 children)</td>
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<td></td>
<td>Exposed children (8...80)</td>
<td>Drinking water Comparison of groups with adequate (&gt; 800 mg/day) and inadequate (&lt; 300 mg/day) dietary calcium intake</td>
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<td>1.5-25 mg/L Since birth</td>
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<td>Comparison of groups with adequate (&gt; 800 mg/day) and inadequate (&lt; 300 mg/day) dietary calcium intake</td>
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<td>2.4, 4.6, 5.6, and 13.5 mg/L</td>
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<td>Since birth [0.25-0.41, 0.40-0.67, 0.48-0.80, and 1.1-1.8 mg/kg/day]§</td>
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<td>Lifelong</td>
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<td></td>
<td></td>
<td>High plasma fluoride, alkaline phosphatase, osteocalcin, PTH, and 1,25(OH2)D3; normal or elevated plasma calcitonin; normal plasma calcium, magnesium, phosphorus, and 25-(OH)D. Combination of fluoride exposure and calcium deficiency led to more severe effects of fluoride, metabolic bone diseases, and bone deformities. Toxic effects of fluoride occur at a lower concentration of fluoride intake (&gt;2.5 mg/day) when there is a calcium deficiency; fluoride exaggerates the metabolic effects of calcium deficiency on bone.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India, children aged 6-12 in four regions (18-30 kg, 50 children per village) Cross-sectional cohort study; random selection of subjects; subjects grouped by location (water fluoride concentration); individual estimates of fluoride intake, measurements of serum and urinary fluoride, other end points; results reported by group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drinking water Calcium intake considered adequate (S.K. Gupta, Satellite Hospital, Banipark, Jaipur, personal communication, December 11, 2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum calcium concentrations within normal range for all groups; serum PTH concentrations elevated in two highest groups; serum PTH correlated with fluoride intake and with severity of clinical and skeletal fluorosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gupta et al. 2001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE E-13 Continued

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose[^a] and Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, 1 adult female Case report</td>
<td>Drinking water “8.4 times above the normal”</td>
<td>Chronic</td>
<td>Fluorosis, leading to secondary hyperparathyroidism manifesting as osteomalacia and a resorptive cavity in the head and neck of the femur; low serum calcium, elevated serum alkaline phosphatase; serum and urine fluoride “86 and 63 times above the normal.”</td>
<td>Chadha and Kumar 2004</td>
</tr>
</tbody>
</table>

[^a]: Information in brackets was calculated from information given in the papers or as otherwise noted.

[^b]: Juncos and Donadio (1972) described two patients with renal insufficiency and systemic fluorosis; PTH was not reported for the second patient.

[^c]: Based on consumption of 2 L of drinking water per day by a 60-kg adult.

[^d]: Based on 60-kg body weight.

[^e]: Based on 30- to 35-kg body weight for the younger children and 50- to 60-kg weight for the older children and mother.

[^f]: Based on consumption of 1-2 L of drinking water per day by a 20- to 40-kg child.

[^g]: Based on mean intakes (mg/day) for 18- to 30-kg children.

**ABBREVIATIONS:** 25(OH)D, 25-hydroxy vitamin D; 1,25(OH)₂D, 1,25-dihydroxy vitamin D.
## TABLE E-14 Summary of Selected Findings for Children in Four Villages

<table>
<thead>
<tr>
<th>Village</th>
<th>Fluoride in Drinking Water, mg/L</th>
<th>Fluoride Intake, mg/day</th>
<th>Serum Fluoride, mg/L</th>
<th>Urinary Fluoride, mg/L</th>
<th>Serum Calcium, mg/dL</th>
<th>IPTHc, pM/L</th>
<th>Enamel Fluorosis Scored</th>
<th>Clinical Fluorosisc</th>
<th>Skeletal Fluorosisf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsagar ki Dhani</td>
<td>2.4</td>
<td>7.35 (1.72)</td>
<td>0.79 (0.21)</td>
<td>9.45 (4.11)</td>
<td>9.23 (1.89)</td>
<td>31.64 (2.82)</td>
<td>2.71 (1.09)</td>
<td>0.95 (0.22)</td>
<td>0.68 (0.67)</td>
</tr>
<tr>
<td>Rampura</td>
<td>4.6</td>
<td>11.97 (1.8)</td>
<td>1.10 (0.58)</td>
<td>15.9 (9.98)</td>
<td>10.75 (1.66)</td>
<td>40.98 (26.9)</td>
<td>1.73 (1.09)</td>
<td>1.00 (0.00)</td>
<td>0.50 (0.61)</td>
</tr>
<tr>
<td>Shivdaspuras</td>
<td>5.6</td>
<td>14.45 (3.19)</td>
<td>1.10 (0.17)</td>
<td>17.78 (7.77)</td>
<td>9.68 (0.99)</td>
<td>75.07 (31.75)</td>
<td>2.44 (1.32)</td>
<td>1.00 (0.00)</td>
<td>0.79 (0.91)</td>
</tr>
<tr>
<td>Raipuria</td>
<td>13.6</td>
<td>32.56 (9.33)</td>
<td>1.07 (0.17)</td>
<td>14.56 (7.88)</td>
<td>10.39 (1.44)</td>
<td>125.10 (131.14)</td>
<td>3.43 (1.70)</td>
<td>1.51 (0.51)</td>
<td>0.95 (1.12)</td>
</tr>
</tbody>
</table>

a Mean (standard deviation) of 50 children per village, ages 6-12, body weight 18-30 kg.
b Total from food and water.
c PTH, midmolecule fragment; normal range, 48.1 ± 11.9 pM/L.
d Grading of enamel fluorosis: 0, normal; 0.5 questionable fluorosis; 1, very mild fluorosis; 2, mild fluorosis; 3, moderate fluorosis; 4 severe fluorosis (defined in more detail by Gupta et al. 2001).
e Clinical (nonskeletal) fluorosis grading: 1, mild; 2, moderate; 3, severe (defined in more detail by Gupta et al. 2001).
f Skeletal (radiological) fluorosis grading: 1, mild; 2, moderate; 3, severe (defined in more detail by Gupta et al. 2001).

<table>
<thead>
<tr>
<th>Species</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongolian gerbil (<em>Meriones unguiculatus</em>; males and females, from birth)</td>
<td>Fluoride in feed (primarily); oral administration of fluoride through 24 days for high-fluoride group</td>
<td>Low-fluoride group, 7 mg/kg/feeding after age 24 days [0.7 mg/kg/day]</td>
<td>Birth through 28 weeks 24-hour urinary 6-sulfatoxymelatonin measured at 7, 9, 11.5, 16, 28 weeks</td>
</tr>
<tr>
<td>Humans (female; 233 in Newburgh, NY; 172 in Kingston, NY) Ecologic study; most of the eligible children in both cities; nonblinded</td>
<td>Fluoride in drinking water</td>
<td>Newburgh, 1.2 mg/L [0.01-0.2 mg/kg/day]</td>
<td>Up to 10 years (ages 7-18 at time of study; ages at beginning of exposure varied from prenatal to 9 years)</td>
</tr>
<tr>
<td>Humans (female; 337 in Kunszentmárton and 467 in Kiskunmajsa, ages 10-19.5 at time of study) Ecologic study; probably included most of the eligible children in both cities; nonblinded</td>
<td>Fluoride in drinking water (probably natural fluoride)</td>
<td>Kunszentmárton, 1.09 mg/L Kiskunmajsa, 0.17 mg/L [0.01-0.2 mg/kg/day versus 0.001-0.02 mg/kg/day]</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

\(^a\)Information in brackets was calculated from information given in the papers or as otherwise noted.

\(^b\)Based on estimated feed consumption of about 10% of body weight per day.

\(^c\)High-fluoride group was given 50 mg/L in drinking water during 24-hour metabolism studies when usual feed was not given.

\(^d\)Estimated fluoride intakes based on ranges of weight and water consumption for children aged 0-18 and fluoride concentration of 1.2 mg/L in drinking water; higher fluoride intakes are associated with the smallest children or the highest water intakes. Some individual intakes could have been lower or higher than the range shown.
### TABLE E-15 Effects of Fluoride on Pineal Function in Animal and Human Studies

<table>
<thead>
<tr>
<th>Species</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Exposure Duration</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongolian gerbil ( repeatedly)</td>
<td>Fluoride in feed (primarily); oral administration of fluoride through 24 days for high-fluoride group</td>
<td>Low-fluoride group, 7 mg/kg feed after age 24 days [0.7 mg/kg/day]</td>
<td>Birth through 28 weeks</td>
<td>6-sulfatoxymelatonin measured at 7, 9, 11.5, 16, 28 weeks</td>
<td>Luke 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-fluoride group, 2.3 mg/kg/day orally, 5 days/week through age 24 days; 37 mg/kg feed thereafter [3.7 mg/kg/day]</td>
<td></td>
<td>Altered rhythms and peaks of melatonin production; significantly lower pineal melatonin production in prepubescent gerbils in high-fluoride than in low-fluoride group. Sexual maturation in females occurred earlier in high-fluoride group (79% versus 42% showing vaginal opening at 7 weeks and 70% versus 16% showing differentiated ventral glands at 11.5 weeks). Lower testicular weight at 16 weeks in males. At 28 weeks, fluoride concentration in trabecular bone ash was 600-700 mg/kg in low-fluoride animals and 2,800 mg/kg in high-fluoride animals.</td>
<td></td>
</tr>
<tr>
<td>Humans (female; 233 in Newburgh, NY; 172 in Kingston, NY)</td>
<td>Fluoride in drinking water</td>
<td>Newburgh, 1.2 mg/L [0.01-0.2 mg/kg/day]</td>
<td>Up to 10 years (ages 7-18 at time of study; ages at beginning of exposure varied from prenatal to 9 years)</td>
<td>Average age at menarche 12 years in Newburgh, versus 12 years 5 months in Kingston; described as not statistically significant. At time of study, 35.2% in Newburgh and 35.0% in Kingston were past menarche (adjusted for age distribution). Distributions of actual menarcheal age not available. Girls exposed since birth or before had not yet reached menarche.</td>
<td>Schlesinger et al. 1956</td>
</tr>
<tr>
<td>Humans (female; 337 in Kunszentmárton and 467 in Kiskunmajsa, ages 10-19.5 at time of study)</td>
<td>Fluoride in drinking water (probably natural fluoride)</td>
<td>Kunszentmárton, 1.09 mg/L Kiskunmajsa, 0.17 mg/L [0.01-0.2 mg/kg/day versus 0.001-0.02 mg/kg/day]</td>
<td>Lifelong Median value of menarcheal age; 12.779 years in Kunszentmárton and 12.79 years in Kiskunmajsa; distributions of actual menarcheal age not available. Distributions of the frequency of girls having reached menarche by the time of the study show, for most age groups below 15 years, higher likelihood of having reached menarche for Kunszentmárton than for Kiskunmajsa (data were not adjusted for different age distributions in the two towns). Of those reporting having reached menarche by the time of the study (159 in Kunszentmárton and 270 in Kiskunmajsa), the youngest were 10 (1 girl), 11 (2 girls), and 11.5 (6 girls) in Kunszentmárton (8.0% of the total in the 10-11.5 age groups, 5.7% of all postmenarcheal girls) and 11.5 (5 girls) in Kiskunmajsa (4.7% of the total in the 10-11.5 age groups, 1.9% of all postmenarcheal girls).</td>
<td>Farkas et al. 1983</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated as a factor of 10 lower than for a fluoride concentration of 1.2 mg/L. Some individual intakes could have been lower or higher than the range shown.

*Ranges assumed to be close to those given for Schlesinger et al. (1956) above. Some individual intakes could have been lower or higher than the ranges shown.
### TABLE E-16 Effects of Fluoride on Other Endocrine Organs in Experimental Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose$^a$</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits (young adult)</td>
<td>Intravenous</td>
<td>3 mg/kg/day</td>
<td>2 months</td>
</tr>
<tr>
<td>Rats (Long-Evans; 2 groups, each with 10 experimental and 5 control; age 49 or 52 days at start, 160-180 g)</td>
<td>Intraperitoneal (controls injected with NaCl)</td>
<td>Acute, 406.47 mg, NaF total [average dose, 68 mg/kg/day]$^b$</td>
<td>Acute, 15 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic, 1131.65 mg of NaF total [average dose, 18 mg/kg/day]$^b$</td>
<td>Chronic, 100 days</td>
</tr>
<tr>
<td>Rats (Hebrew University albino, males; infants at start, 30-32 g)</td>
<td>Drinking water</td>
<td>0.55, 1, or 10 mg/L, [0.055, 0.1, and 1 mg/kg/day]$^c$</td>
<td>9 months</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, males, 325-350 g)</td>
<td>Intravenous</td>
<td>6 mg/kg/hour</td>
<td>3 hours</td>
</tr>
<tr>
<td>Rats (Wistar)</td>
<td>Drinking water and diet</td>
<td>Water: 0, 1, 5, 10, 50, 100, or 200 mg/L. Diet: 0.31 or 34.5 ppm [0, 0.1, 0.5, 1, 5, 10, or 20 mg/kg/day from water and 0.025 or 2.8 mg/kg/day from feed]$^d$</td>
<td>54-58 days</td>
</tr>
<tr>
<td>Rats (Wistar albino, males, 95-105 g)</td>
<td>Intraperitoneal (controls injected with NaCl)</td>
<td>15.8 mg/kg (35 mg/kg of NaF)</td>
<td>Single dose</td>
</tr>
<tr>
<td>Rats (inbred strain IIM, females, 180-220 g)</td>
<td>Oral administration of NaF by gastric tube</td>
<td>7.6 mg/kg</td>
<td>Single dose, after fasting for 24 hours</td>
</tr>
</tbody>
</table>
## Effects of Fluoride on Other Endocrine Organs in Experimental Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Effects References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits (young adult)</td>
<td>Intravenous</td>
<td>3 mg/kg/day</td>
<td>2 months</td>
</tr>
<tr>
<td>Rats (Long-Evans; 2 groups, each with 10 experimental and 5 control; age 49 or 52 days at start, 160-180 g)</td>
<td>Intraperitoneal (controls injected with NaCl)</td>
<td>Acute: 406.47 mg, NaF total [average dose, 68 mg/kg/day]</td>
<td>Chronic: 1131.65 mg of NaF total [average dose, 18 mg/kg/day]</td>
</tr>
<tr>
<td>Rats (Hebrew University albino, males; infants at start, 30-32 g)</td>
<td>Drinking water</td>
<td>0.55, 1, or 10 mg/L [0.055, 0.1, and 1 mg/kg/day]</td>
<td>9 months</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, males, 325-350 g)</td>
<td>Intravenous</td>
<td>6 mg/kg/hour</td>
<td>3 hours</td>
</tr>
<tr>
<td>Rats (Wistar)</td>
<td>Drinking water and diet</td>
<td>Water: 0, 1, 5, 10, 50, 100, or 200 mg/L</td>
<td>Diet: 0.31 or 34.5 ppm [0, 0.1, 0.5, 1, 5, 10, or 20 mg/kg/day from water and 0.025 or 2.8 mg/kg/day from feed]</td>
</tr>
<tr>
<td>Rats (Wistar albino, males, 95-105 g)</td>
<td>Intraperitoneal (controls injected with NaCl)</td>
<td>15.8 mg/kg (35 mg/kg of NaF) Single dose</td>
<td>Elevated serum glucose and enhanced glucose-6-phosphate dehydrogenase (G6PD) activities in liver and kidney; attributed to stimulation of adrenal function, both medullary and cortical; changes in glucose concentrations and G6PD activities suppressed by adrenalectomy but not by thyroid-parathyroidectomy. Immediate fall in insulin concentrations (to 50% of basal concentration after 15 minutes) and consequent increase in glycemia (peak at about 1 1/2 hours), returned to normal in 4-5 hours. Decreased insulin response to glucose challenge when fluoride administered 15 minutes before glucose challenge (versus together with or immediately after). Appeared to be direct effect on insulin secretion, not on insulin receptors; hypoglycemic response to exogenous insulin was not impaired by pretreatment with fluoride. Plasma fluoride: 0.1-0.3 mg/L (5-15 µmol/L).</td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (female, IIM line, age 21 days at start)</td>
<td>Drinking water (NaF)</td>
<td>95 mg/L (5 mmol/L) [10 mg/kg/day]</td>
<td>100 days</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, male, 40-50 g weanlings at start, 68-77 animals per group)</td>
<td>Drinking water</td>
<td>5, 15, or 50 mg/L [0.26-0.45, 0.69-1.31, and 2.08-3.46 mg/kg/day] (changing with increasing body weight)</td>
<td>3, 6, 12, or 18 months</td>
</tr>
<tr>
<td>Rats (female, IIM line, age 21 days at start)</td>
<td>Drinking water (NaF)</td>
<td>95 mg/L (5 mmol/L) [10 mg/kg/day]</td>
<td>3 months</td>
</tr>
<tr>
<td>Rats (Zucker, males, normal and fatty diabetic, age-matched, 8 weeks old at start of study, initial weights 282 g for controls and 351 g for diabetics)</td>
<td>Drinking water (NaF) (minimal contribution from feed)</td>
<td>0, 5, 15, or 50 mg/L in drinking water (&lt;1.2 ppm in feed) [Control: 0.05, 0.31, 0.85, and 2.8 mg/kg/day Diabetic: 0.09, 2.0, 6.0, and 15.5 mg/kg/day]</td>
<td>3 or 6 months</td>
</tr>
</tbody>
</table>

Rigalli et al. 1992

Effects on glucose homeostasis not seen with equivalent (5 mmol/L) amount of sodium monofluorophosphate (MFP); plasma diffusable fluoride always below 0.04 mg/L (2 µmol/L); protein-bound MFP did not affect glucose homeostasis.

Rigalli et al. 1995

Water intake and fluoride intake approximately 6 times higher in diabetics than in controls for a given fluoride concentration; fluoride absorption about 75% in diabetics versus 63% in controls; fluoride retention about 40% (39-42%) in diabetics versus increasing with fluoride dose (27-45%) in controls. Plasma and tissue fluoride concentrations increased with fluoride dose, significantly higher for diabetics than for controls.

Dunipace et al. 1995

Reported doses for control rats (mg/kg/day): 0.33 for 5 mg/L and 3.04 or 50 mg/L; for diabetic rats, 1.99 for 5 mg/L and 16.26 for 50 mg/L.
Species and Strain Exposure Conditions Concentration or Dose Exposure Duration Effects Reference

Rats (female, IIM line, age 21 days at start) Drinking water (NaF) 95 mg/L (5 mmol/L) [10 mg/kg/day] 100 days Subtle disturbance of glucose tolerance as shown by glucose tolerance tests, associated with period of elevated fluoride concentrations in plasma and soft tissue (deterioration of glucose tolerance for about 50 days and then normalization by 100 days, when maximum bone mass was achieved and plasma fluoride returned to normal concentrations). Bone mass higher 6-12% greater in fluoride-treated animals (depending on portion of skeleton considered). Bone fluoride (ppm in ash): controls, 1,160-1,410; treated, 6,880-8,550 (depending on portion of skeleton considered).

“No significant effect” on fasting plasma glucose concentrations; specific data by treatment group not reported.

Rigalli et al. 1992

Rats (Sprague-Dawley, male, 40-50 g weanlings at start, 68-77 animals per group) Drinking water 5, 15, or 50 mg/L [0.26-0.45, 0.69-1.31, and 2.08-3.46 mg/kg/day] (changing with increasing body weight) 3, 6, 12, or 18 months "No significant effect" on fasting plasma glucose concentrations; specific data by treatment group not reported.

Dunipace et al. 1995

Rats (female, IIM line, age 21 days at start) Drinking water (NaF) 95 mg/L (5 mmol/L) [10 mg/kg/day] 3 months Abnormal glucose tolerance tests when plasma diffusible fluoride exceeds 0.1 mg/L (5 µmol/L). Effects on glucose homeostasis not seen with equivalent (5 mmol/L) amount of sodium monofluorophosphate (MFP); plasma diffusible fluoride always below 0.04 mg/L (2 µmol/L); protein-bound MFP did not affect glucose homeostasis.

Rigalli et al. 1995

Rats (Zucker, males, normal and fatty diabetic, age-matched, 8 weeks old at start of study, initial weights 282 g for controls and 351 g for diabetics) Drinking water (NaF) (minimal contribution from feed) 0, 5, 15, or 50 mg/L in drinking water (<1.2 ppm in feed) [Control: 0.05, 0.31, 0.85, and 2.8 mg/kg/day Diabetic: 0.09, 2.0, 6.0, and 15.5 mg/kg/day] Reported doses for control rats (mg/kg/day): 0.33 for 5 mg/L and 3.04 or 50 mg/L; for diabetic rats, 1.99 for 5 mg/L and 16.26 for 50 mg/L 3 or 6 months Water intake and fluoride intake approximately 6 times higher in diabetics than in controls for a given fluoride concentration; fluoride absorption about 75% in diabetics versus 63% in controls; fluoride retention about 40% (39-42%) in diabetics versus increasing with fluoride dose (27-45%) in controls. Plasma and tissue fluoride concentrations increased with fluoride dose, significantly higher for diabetics than for controls.

Plasma fluoride (mg/L) in controls: 0.008-0.010, 0.015-0.017, 0.029, and 0.072-0.082; in diabetics: 0.0097-0.012, 0.036-0.046, 0.10-0.12, and 0.26-0.36. Bone fluoride (ppm in ash) in controls: 171-194, 410-560, 872-1,330, and 2,500-3,600; in diabetics: 200-310, 1,000-2,000, 2,700-4,700, and 6,800-9,500. Same mean blood glucose value (453.5 ± 8.2 mg/dL) given for initial and final values in diabetic rats—one of them is probably not correct; for controls, initial value of 121.9 ± 1.7 mg/dL and final value of 129.6 ± 1.7 mg/dL. Markers examined: plasma urea, glucose (nonfasting), creatinine, calcium, phosphorus, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, glutamate oxaloacetate transaminase; urine urea, creatinine; creatinine clearance; histological evaluations; bone marrow sister chromatid exchanges. Significant differences in many parameters between normal and diabetic animals; with respect to fluoride intake, significant differences only for diabetic rats with fluoride at 50 mg/L (lower plasma cholesterol, higher total protein in plasma, increased width of tibial cortex).

Dunipace et al. 1996

continued
### TABLE E-16 Continued

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose*</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits (Dutch-Belted, female, 3 1/2 months old at start, 1.55 kg)</td>
<td>Drinking water</td>
<td>0 and 100 mg/L [7-10.5 mg/kg/day]</td>
<td>6 months</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, male, 30-40 g weanlings at start, 432 animals total)</td>
<td>Drinking water</td>
<td>5, 15, or 50 mg/L [0.5, 1.5, or 5 mg/kg/day]</td>
<td>16 or 48 weeks</td>
</tr>
<tr>
<td>Rats (Charles River, Wistar, females, normal and with streptozotocin-induced diabetes, 8 per group)</td>
<td>Drinking water and feed (NaF in drinking water)</td>
<td>Drinking water: Groups C and D, 0 mg/L Groups F10 and DF10, 10 mg/L Group FF, adjusted to match fluoride intake of DF10 Feed: 13 ppm (all groups) [C: 1.0-1.5 mg/kg/day F10: 2.1-2.9 mg/kg/day D: 2.2-2.5 mg/kg/day DF10: 8.4-18.6 mg/kg/day FF: 8.3-11.8 mg/kg/day]</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Horses (6 total, thoroughbreds, average age 5 years, average weight 509 kg, euthanized at end of experiment)</td>
<td>Sevoflurane anesthesia</td>
<td>Not available</td>
<td>Mean, 18.5 hours</td>
</tr>
</tbody>
</table>

Notes:
- *Fluoride concentration in drinking water.
- **Table E-11**

**References:**
- Turner et al. 1997
- Dunipace et al. 1998
- Boros et al. 1998
- Driessen et al. 2002

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### APPENDIX E

#### TABLE E-16

<table>
<thead>
<tr>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistically significant ($P &lt; 0.05$) increase in serum glucose (17%). Increased IGF-1 (40%). Insulin or other regulators of serum glucose were not measured. No effect of fluoride on serum urea, creatinine, phosphorus, total protein, albumin, or bilirubin; serum glutamate oxaloacetate transaminase; or total alkaline phosphatase. Increased serum fluoride (0.728 versus 0.0441 mg/L) and bone fluoride (6,650-7,890 versus 850-1,150 ppm in ash). No significant effect on fasting plasma glucose; specific data by fluoride treatment group not reported. Combination of general malnutrition and calcium deficiency was not examined.</td>
<td>Turner et al. 1997</td>
</tr>
</tbody>
</table>

Normal rats had similar intakes of feed and water regardless of fluoride intake; final body weights were similar. Diabetic rats had 3-5 times higher water intake than normal rats and almost twice the feed intake; final body weights for group D were lower than for normal rats; final body weights for group DF$_{10}$ were lower than initial body weights. Increase in overall severity of diabetes and higher fasting blood glucose concentrations in fluoride-treated diabetic rats; about 400 mg/dL (22 mM/L) in DF$_{10}$ versus 250 mg/dL (14 mM/L) in D and 90 mg/dL (5 mmol/L) in C, F$_{10}$, and FF. Plasma fluoride (approximate, mg/L): C, 0.029; F$_{10}$, 0.038; D, 0.038; DF$_{10}$, 0.095; FF, 0.057. Bone (femoral) fluoride (approximate, ppm in ash): C, 400; F$_{10}$, 600; D, 400; DF$_{10}$, 1000; FF, 1900. Fluoride treatment in nondiabetic rats did not cause significant alteration of blood glucose concentrations. | Boros et al. 1998 |

Mean plasma fluoride after 8 hours was 0.7-0.9 mg/L (38-45 µmol/L). Total and ionized calcium decreased over time; ionized calcium remained within normal limits; total calcium below normal values after 2 hours. Serum glucose concentrations increased throughout, exceeding normal concentrations at 6 hours and thereafter, but within the values commonly observed during general inhalation anesthesia in horses; glucosuria also present after 10 hours. | Driessen et al. 2002 |
### TABLE E-16 Continued

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (Wistar, adult females, 150-170 g at start; fluoride administered during pregnancy and lactation)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>NaF orally by feeding tube</td>
<td>40 mg/kg/day NaF (18 mg/kg/day fluoride to the mothers)</td>
<td>Day 6 of gestation through day 21 of lactation</td>
</tr>
<tr>
<td>Rats (Wistar FL, males, 14 weeks old, 8 treated, 10 controls)</td>
<td>Intraperitoneal injection</td>
<td>35 mg/kg NaF (15.8 mg/kg fluoride) in physiological saline Controls, saline only</td>
<td>Single dose, sacrificed 90 minutes later</td>
</tr>
</tbody>
</table>

<sup>a</sup>Information in brackets was calculated from information given in the papers or as otherwise noted.

<sup>b</sup>Based on average of initial and final mean body weights.

<sup>c</sup>Based on water consumption of about 10% of body weight, with no significant differences in body weight with fluoride intake.

<sup>d</sup>Based on water consumption of about 10% of body weight and feed consumption of about 8% of body weight, with no significant differences in body weight with fluoride intake.

<sup>e</sup>Based on final (6-month) mean body weights of 508.8 g for controls and 445.4 g for diabetics, with pretermination (3- and 6-month combined) metabolic data for fluoride intake.

<sup>f</sup>Plasma fluoride (µmol/L) in controls: 0.42-0.54, 0.8-0.9, 1.5, and 3.8-4.3; in diabetics: 0.51-0.65, 1.9-2.4, 5.5-6.1, and 13.6-19.2

<sup>g</sup>Based on average daily water consumption of 163 mL, mean initial weight of 1.55 kg, and mean final weight of 2.33 kg for the fluoride-treated group.

<sup>h</sup>Serum fluoride: 38.31 versus 2.32 µmol/L.

<sup>i</sup>Based on average daily fluoride intake for days 1-4 with average initial body weight for all groups and average daily intake for days 15-21 with average final body weight for the group.

<sup>j</sup>Plasma fluoride (approximate, µmol/L): C, 1.5; F<sub>10</sub>, 2; D, 2; DF<sub>10</sub>, 5; FF, 3.

<sup>k</sup>In many mammalian species, maternal fluoride exposures are not well reflected by fluoride concentrations in milk; therefore, the impacts of fetal exposure and of reduced milk production by the mothers must also be considered.
## APPENDIX E

### TABLE E-16 Continued

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<th>Effects</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Marked hypoglycemia in mothers and offspring, attributed to reduced feed consumption.</td>
<td>Verma and Guna Sherlin 2002a</td>
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<tr>
<td>Reduced serum protein content, significant increases in serum sodium and potassium.</td>
<td></td>
</tr>
<tr>
<td>Significant recovery on withdrawal of NaF or supplementation with vitamins C, D, and E.</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia (47% increase), accompanied by impairment in renal function, decreased calcium concentrations (13%).</td>
<td>Grucka-Mamczar et al. 2005</td>
</tr>
</tbody>
</table>

In many mammalian species, maternal fluoride exposures are not well reflected by fluoride concentrations in milk; therefore, the impacts of fetal exposure and of reduced milk production by the mothers must also be considered.

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[Fluoride in Drinking Water: A Scientific Review of EPA’s Standards](http://www.nap.edu/catalog/11571.html)
### TABLE E-17 Effects of Fluoride on Other Endocrine Organs in Humans

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose&lt;sup&gt;a&lt;/sup&gt; and Exposure Duration</th>
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</thead>
<tbody>
<tr>
<td>76 male and female inmates of Japanese mental hospital</td>
<td>Thought to be from pesticide use</td>
<td>Not available Chronic</td>
</tr>
<tr>
<td>Observational study; summary of cases; cross-sectional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41 Russian males with fluorosis, ages 33-45, 19 controls (no contact with fluorine compounds)</td>
<td>Occupational exposure</td>
<td>Not available &gt;15 years for some</td>
</tr>
<tr>
<td>Case-control study; cross-sectional; full details not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteers in Argentina, 6 adults</td>
<td>Oral administration to fasting persons</td>
<td>27 mg of fluoride (60 mg of NaF) [0.4 mg/kg]&lt;sup&gt;b&lt;/sup&gt; Single dose</td>
</tr>
<tr>
<td>Experimental study; subjects included the authors of the report and members of their laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 young adults (14 males, 11 females) in India with endemic fluorosis (skeletal and enamel), ages 15-30 years (nonobese, nonsmokers, no personal or family history of diabetes mellitus or hypertension)</td>
<td>Drinking water</td>
<td>2-13 mg/L in drinking water [0.067-0.43 mg/kg/day]&lt;sup&gt;c&lt;/sup&gt; Controls: &lt; 1 mg/L [&lt; 0.03 mg/kg/day]&lt;sup&gt;c&lt;/sup&gt; Since birth</td>
</tr>
<tr>
<td>25 controls with normal fluoride intake (age, sex, and body mass index matched; comparable social and working conditions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control study; cross-sectional for all; longitudinal for subjects initially found to have impaired glucose tolerance; tests were repeated after 6 months on a low-fluoride water source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland, residents of Skawina (living in the vicinity of an aluminum smelter) and Chorzów (employed in any of 3 industries); approximately 50 individuals per group (approximately 200 total)</td>
<td>Airborne fluorides</td>
<td>8-10 times the Maximum Allowable Concentration for fluoride of 1.6 µg/m³ (12.8-16 µg/m³)</td>
</tr>
<tr>
<td>Ecologic measure of exposure (exposure to environmental fluorides from industrial pollution)</td>
<td>Skawina: chronic exposure to fluorine compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chorzów: chronic exposure to environmental fluorides and other toxic compounds</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Concentration or dose is given in units of mg/L for drinking water and mg/kg for oral administration. For airborne fluorides, the concentration is given in units of µg/m³.

<sup>b</sup> The concentration of NaF is given in units of mg/kg.

<sup>c</sup> The concentration of fluoride is given in units of mg/kg/day.
TABLE E-17 Effects of Fluoride on Other Endocrine Organs in Humans

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>76 male and female inmates of Japanese mental hospital</td>
<td>Observational study; summary of cases; cross-sectional</td>
<td>Not available</td>
<td>Chronic Endocrine disturbances including melanosis in 20 of 76 patients; attributed to dysfunction of parathyroids and adrenals, reversed upon treatment for chronic fluorine poisoning.</td>
<td>Spira 1962</td>
</tr>
<tr>
<td>41 Russian males with fluorosis, ages 33-45, 19 controls (no contact with fluorine compounds)</td>
<td>Occupational exposure</td>
<td>Not available</td>
<td>Elevated follicle-stimulating hormone and decreased testosterone in blood in all men with fluorosis; elevated blood luteinizing hormone in men with long-term exposure (&gt;15 years).</td>
<td>Tokar’ and Savchenko 1977</td>
</tr>
<tr>
<td>Volunteers in Argentina, 6 adults</td>
<td>Experimental study; subjects included the authors of the report and members of their laboratory</td>
<td>Oral administration to fasting persons</td>
<td>After 1 hour, significant fall of plasma insulin concentrations and increased fluoride; reduced insulin response to glucose challenge. Plasma fluoride: 0.1-0.3 mg/L (5-15 µmol/L).</td>
<td>Rigalli et al. 1990</td>
</tr>
<tr>
<td>25 young adults (14 males, 11 females) in India with endemic fluorosis (skeletal and enamel), ages 15-30 years (nonobese, nonsmokers, no personal or family history of diabetes mellitus or hypertension) 25 controls with normal fluoride intake (age, sex, and body mass index matched; comparable social and working conditions)</td>
<td>Exposure to drinking water</td>
<td>Drinking water 2-13 mg/L in drinking water [0.067-0.43 mg/kg/day] Controls: &lt; 1 mg/L [&lt; 0.03 mg/kg/day]</td>
<td>Impaired glucose tolerance (IGT) in 40% (6 males, 4 females); fasting serum fluoride concentrations positively correlated ( P &lt; 0.01 ) with area under glucose curve in those 10; effect appeared to be reversible on provision of drinking water with “acceptable” fluoride concentrations (&lt;1 mg/L). For all 25 endemic fluorosis patients, significant positive correlation between serum fluoride and fasting serum immunoreactive insulin; significant negative correlation between serum fluoride and fasting glucose:insulin ratio. Normal serum calcium, inorganic phosphorus, and vitamin D; elevated serum alkaline phosphatase in patients with endemic fluorosis. Urine fluoride (mg/L): fluorosis patients, 2-8; controls, 0.2-0.5. Serum fluoride (mg/L): patients with IGT, 0.08 ± 0.04; patients with normal glucose tolerance, 0.02 ± 0.01; controls, 0.01 ± 0.009; IGT patients after 6 months on low-fluoride water, 0.02 ± 0.01. Excessive excretion of fluorides in urine (53-100% with urine fluoride &gt; 2.3 mg/L; for Skawina, mean = 5.6 mg/L; SD = 2.5, n = 46), associated with a decrease in urine and erythrocyte magnesium concentrations (36-65% with urine magnesium &lt; 5.4 mg/L); increased blood glucose and lactate concentrations, which were normalized by magnesium supplementation. For Skawina, 74% had blood glucose results above the norm (70-100 mg/dL or 3.89-5.55 mmol/L; n = 42).</td>
<td>Trivedi et al. 1993</td>
</tr>
<tr>
<td>Poland, residents of Skawina (living in the vicinity of an aluminum smelter) and Chorzów (employed in any of 3 industries); approximately 50 individuals per group (approximately 200 total)</td>
<td>Ecologic measure of exposure (exposure to environmental fluorides from industrial pollution)</td>
<td>Airborne fluorides Skawina: chronic exposure to fluorine compounds Chorzów: chronic exposure to environmental fluorides and other toxic compounds 8-10 times the Maximum Allowable Concentration for fluoride of 1.6 µg/m³ (12.8-16 µg/m³)</td>
<td>Excessive excretion of fluorides in urine (53-100% with urine fluoride &gt; 2.3 mg/L; for Skawina, mean = 5.6 mg/L; SD = 2.5, n = 46), associated with a decrease in urine and erythrocyte magnesium concentrations (36-65% with urine magnesium &lt; 5.4 mg/L); increased blood glucose and lactate concentrations, which were normalized by magnesium supplementation. For Skawina, 74% had blood glucose results above the norm (70-100 mg/dL or 3.89-5.55 mmol/L; n = 42).</td>
<td>Kedryna et al. 1993</td>
</tr>
</tbody>
</table>

continued
TABLE E-17 Continued

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose(^a) and Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S., female osteoporosis patients (patients with previous history of hyperparathyroidism and several other conditions were excluded) Initial recruitment included 203 in-state patients from previous fluoride trials and 95 controls who had not taken fluoride; of these, 40 fluoride patients and 43 controls were scheduled for appointments; 15 fluoride patients were no longer taking fluoride or failed the appointments; 5 controls failed the appointments; final study included 25 fluoride patients and 38 controls (mean ages, 70.1 for fluoride group, 69.5 for controls) Cross-sectional study; fluoride-treated patients and non-fluoride-treated controls recruited from database of osteoporosis patients of one investigator; fasting samples; analyses of drinking water, blood, and urine performed blindly; results reported as means of groups and as number outside the normal range for the parameter; urine and plasma fluoride clearly different between groups; no significant difference in mean water fluoride concentrations See also Table E-12</td>
<td>Slow-release sodium monofluorophosphate plus 1,500 mg/day calcium carbonate Most controls (n = 38) had calcium supplementation</td>
<td>23 mg/day (mean dose) [0.33 mg/kg/day](^b) 1.4-12.6 years (mean, 4.2 years)</td>
</tr>
<tr>
<td>China, healthy adults (approximately 120 per group, with either normal or inadequate nutritional intakes; mean ages of groups, 44.9-47.7 years) Cross-sectional cohort study; subjects grouped by location (water fluoride concentration) and nutritional status; populations generally similar (e.g., socially and economically); estimated fluoride intakes and measurements of urine and plasma fluoride and other parameters were made for individuals but results reported only for groups; probably overlap between low (&lt;0.3 mg/L) and middle (around 1 mg/L) fluoride exposure groups for each nutritional category; no mention of whether analyses were performed blindly See also Table E-12</td>
<td>Drinking water Normal nutrition defined as &gt; 75 g/day protein and Ca &gt; 600 mg/day Inadequate nutrition defined as &lt; 60 g/day protein and Ca &lt; 400 mg/day Estimated intakes: 1.70, 3.49, and 14.8 mg/day (normal nutrition); 1.20, 2.64, 15.32 mg/day (inadequate nutrition) At least 35 years of continuous residency in the study area</td>
<td>0.23, 1.02, and 5.03 mg/L (normal nutrition) 0.11, 0.90, and 4.75 mg/L (inadequate nutrition)</td>
</tr>
</tbody>
</table>
### Effects

<table>
<thead>
<tr>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean fasting blood glucose concentrations 104.7 (SD = 53.0) for fluoride-treated group and 95.2 (SD = 10.3) for controls (difference not considered significant); 3 of 25 fluoride-treated individuals outside normal range (versus 1 of 38 controls).</td>
<td>Jackson et al. 1994</td>
</tr>
<tr>
<td>Urine fluoride (mg/L, mean and SD): fluoride group, 9.7 (4.1); controls, 0.8 (0.5); plasma fluoride (mg/L, mean and SD): fluoride group, 0.17 (0.068); controls, 0.019 (0.0076).</td>
<td>Li et al. 1995</td>
</tr>
</tbody>
</table>

No significant differences in mean blood glucose concentrations among groups. Not clear whether samples were fasting or nonfasting.
### TABLE E-17 Continued

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose(^a) and Exposure Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 postmenopausal women in Argentina Experimental study; subjects were members of the authors’ department who were receiving NaF as treatment for osteoporosis and who volunteered to undergo glucose tolerance tests; tests were administered in the fasting state</td>
<td>Treatment for osteoporosis</td>
<td>13.6 mg/day (30 mg/day NaF) [0.23 mg/kg/day](^e) 9 and 24 months</td>
</tr>
<tr>
<td>24 women and 2 men, ages 44-66, former residents of an area of endemic fluorosis in Argentina Ecologic exposure measure; cross-sectional study; fasting blood samples</td>
<td>Drinking water</td>
<td>Not stated Chronic</td>
</tr>
<tr>
<td>U.S., 199 adult volunteers (mean ages of groups, 62.3, 58.6, 57.2 years) Ecologic study; cross-sectional; subjects grouped by location (water fluoride concentration); subjects not randomly selected; nonfasting samples; urine and plasma fluoride concentrations significantly different for groups; study parameters reported by groups; no information on whether analyses were performed blindly See also Table E-12</td>
<td>Drinking water, natural fluoride Dietary calcium and calcium concentrations in drinking water were not discussed</td>
<td>0.2, 1.0, 4.0 mg/L [0.003, 0.01, 0.06 mg/kg/day](^b) At least 30 years of continuous residency in their communities</td>
</tr>
<tr>
<td>160 males ages 20-50 years, in Mexico Ecologic exposure measure based on occupation; exposure groups overlapped; no information on selection of subjects</td>
<td>Drinking water alone for 27 men (low group) Occupational exposure and drinking water for 133 men (high group)</td>
<td>3.0 mg/L in drinking water 2-13 mg/day estimated for low group [0.03-0.19 mg/kg/day](^b) 3.4-27.4 mg/day estimated for high group [0.05-0.39 mg/kg/day](^b) Chronic (at least 1 year for occupational exposure)</td>
</tr>
</tbody>
</table>

\(^a\)Information in brackets was calculated from information given in the papers or as otherwise noted.

\(^b\)Based on 70-kg per person.

\(^c\)Based on consumption of 2 L of drinking water per day by a 60-kg adult.

\(^d\)Reported as 9.0 (3.6) µmol/L for the fluoride group and 1.0 (0.4) µmol/L for the controls.

\(^e\)Based on 60-kg per person.
### Effects of Fluoride Exposure on Glucose Homeostasis and Other Endpoints

<table>
<thead>
<tr>
<th>Study Population(s)</th>
<th>Exposure Conditions</th>
<th>Concentration or Dose</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 postmenopausal women in Argentina</td>
<td>Experimental study; subjects were members of the authors' department who were receiving NaF as treatment for osteoporosis and who volunteered to undergo glucose tolerance tests; tests were administered in the fasting state</td>
<td>Treatment for osteoporosis 13.6 mg/day (30 mg/day NaF) [0.23 mg/kg/day]</td>
<td>Disturbed glucose homeostasis when given glucose tolerance test. Plasma F: 0.11 and 0.13 mg/L (5.6 and 6.7 µM/L).</td>
<td>Rigalli et al. 1995</td>
</tr>
<tr>
<td>24 women and 2 men, ages 44-66, former residents of an area of endemic fluorosis in Argentina</td>
<td>Ecologic exposure measure; cross-sectional study; fasting blood samples</td>
<td>Drinking water Not stated</td>
<td>Inverse relationship between plasma fluoride and area under curve of insulin during a standard glucose tolerance test. Plasma F: 0.01-0.18 mg/L (0.5-9.2 µM/L). Urine F: &gt; 1.1 mg/day.</td>
<td>de la Sota et al. 1997</td>
</tr>
<tr>
<td>U.S., 199 adult volunteers (mean ages of groups, 62.3, 58.6, 57.2 years)</td>
<td>Ecological study; cross-sectional; subjects grouped by location (water fluoride concentration); subjects not randomly selected; nonfasting samples; urine and plasma fluoride concentrations significantly different for groups; study parameters reported by groups; no information on whether analyses were performed blindly</td>
<td>Drinking water, natural fluoride</td>
<td>No significant differences among mean glucose concentrations (nonfasting); all mean values were within normal ranges.</td>
<td>Jackson et al. 1997</td>
</tr>
<tr>
<td>160 males ages 20-50 years, in Mexico</td>
<td>Ecologic exposure measure based on occupation; exposure groups overlapped; no information on selection of subjects</td>
<td>Drinking water alone for 27 men (low group)</td>
<td>Elevated follicle stimulating hormone; decreased testosterone, inhibin B, and prolactin; apparent reduction in sensitivity of the hypothalamic-pituitary axis to negative feedback action from inhibin B. Fluoride exposures of the two groups overlapped, and occupational exposures included other chemicals besides fluoride.</td>
<td>Ortiz-Perez et al. 2003</td>
</tr>
</tbody>
</table>
A Systematic Review of Public Water Fluoridation

Marian McDonagh¹
Penny Whiting¹
Matthew Bradley¹
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Alex Sutton³
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September 2000
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<td>Studies in which fluoridation was initiated</td>
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<td>5.</td>
<td>Objective 2: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?</td>
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We also greatly appreciate the contributions of many scientists and members of the public who submitted papers for inclusion and made valuable comments about the protocol, data extraction tables and results of the review.
This systematic review has been commissioned by the Chief Medical Officer of the Department of
Health to ‘carry out an up to date expert scientific review of fluoride and health’ (Paragraph 9.20, Our
Healthier Nation).

Overall, the aim has been to assess the evidence on the positive and negative effects of population
wide drinking water fluoridation strategies to prevent caries. To achieve this aim five objectives were
identified:

**Objective 1:** What are the effects of fluoridation of drinking water supplies on the incidence of caries?

**Objective 2:** If water fluoridation is shown to have beneficial effects, what is the effect over and above
that offered by the use of alternative interventions and strategies?

**Objective 3:** Does water fluoridation result in a reduction of caries across social groups and between
geographical locations, bringing equity?

**Objective 4:** Does water fluoridation have negative effects?

**Objective 5:** Are there differences in the effects of natural and artificial water fluoridation?

**Methods**

A search of 25 electronic databases (with no language restrictions) and the world-wide-web was
undertaken. Relevant journals and indices were hand searched and attempts were made to contact
authors for further information.

Quality inclusion criteria were based on a pre-defined hierarchy of evidence (A, B, and C). Studies of
efficacy were included if they were of evidence level A or B. In order to allow the broadest search for
evidence on potential adverse effects, studies of all levels of evidence were included. Objective
specific inclusion criteria, based on selection of participants, intervention, outcomes assessed, and
study design appropriate for a given objective were then applied. Study validity was formally assessed
using a published checklist modified for this review (CRD Report 4, 1996).

Inclusion criteria were assessed independently by at least two reviewers. Extraction of data from, and
validity assessment of, included studies was independently performed by two reviewers, and checked
by a third reviewer. Disagreements were resolved through consensus.

Where the data were in a suitable format, measures of effect and 95% confidence intervals (CI) were
plotted. Heterogeneity was investigated by visual examination and statistically using the Q-statistic.
Where no evidence of heterogeneity was found a meta-analysis was conducted to produce a pooled
estimate of the measure of effect. Statistically significant heterogeneity was investigated using meta-
regression. Multiple regression analysis was used to explore the relationship between fluoridation and
fluorosis.

**Results**

214 studies met full inclusion criteria for one or more of the objectives. No randomised controlled trials
of the effects of water fluoridation were found. The study designs used included 45 ‘before and after’
studies, 102 cross-sectional studies, 47 ecological studies, 13 cohort (prospective or retrospective)
studies and 7 case-control studies. Several studies were reported in multiple papers over a number of
years.
Results by Objective

Objective 1

A total of 26 studies of the effect of water fluoridation on dental caries were found. For this objective, the quality of studies found was moderate (no level A studies). A large number of studies were excluded because they were cross-sectional studies and therefore did not meet the inclusion criteria of being evidence level B or above. All but three of the studies included were before-after studies, two included studies used prospective cohort designs, and one used a retrospective cohort design. All before-after studies located by the search were included. The most serious defect of these studies was the lack of appropriate analysis. Many studies did not present an analysis at all, while others only did simple analyses without attempting to control for potentially confounding factors. While some of these studies were conducted in the 1940’s and 50’s, prior to the common use of such analyses, studies conducted much later also failed to use methods that were commonplace at the time of the study.

Another defect of many studies was the lack of any measure of variance for the estimates of decay presented. While most studies that presented the proportion of caries-free children contained sufficient data to calculate standard errors, this was not possible for the studies that presented dmft/DMFT scores. Only four of the eight studies using these data provided estimates of variance.

The best available evidence suggests that fluoridation of drinking water supplies does reduce caries prevalence, both as measured by the proportion of children who are caries free and by the mean change in dmft/DMFT score. The studies were of moderate quality (level B), but of limited quantity. The degree to which caries is reduced, however, is not clear from the data available. The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.6% (interquartile range 5.05, 22.1%). The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth). It is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9). The best available evidence from studies following withdrawal of water fluoridation indicates that caries prevalence increases, approaching the level of the low fluoride group. Again, however, the studies were of moderate quality (level B), and limited quantity. The estimates of effect could be biased due to poor adjustment for the effects of potential confounding factors.

Objective 2

To address this objective, studies conducted after 1974 were examined. While only nine studies were included for Objective 2, these would have been enough to provide a confident answer to the objective’s question if the studies had been of sufficient quality. Since these studies were completed after 1974, one might expect that the validity assessments would be higher than the earlier studies following the introduction of more rigorous study methodology and analytic techniques. However, the average validity checklist score and level of evidence was essentially the same for studies after 1974 as those conducted prior to 1974. Hence, the ability to answer this objective is similar to that in Objective 1.

In those studies completed after 1974, a beneficial effect of water fluoridation was still evident in spite of the assumed exposure to non-water fluoride in the populations studied. The meta-regression conducted for Objective 1 confirmed this finding.

Objective 3

No level A or B studies examining the effect of water fluoridation on the inequalities of dental health between social classes were identified. However, because of the importance of this objective, level C studies conducted in England were included. A total of 15 studies investigating the association of water fluoridation, dental caries and social class in England were identified. The quality of the evidence of the studies was low, and the measures of social class that were used varied. Variance data were not reported in most of these studies, so a statistical analysis was not undertaken.

There appears to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in 5 and 12 year-olds, using the dmft/DMFT measure. This effect was not seen in the proportion of caries-free children among 5 year-olds. The data for the effects in children of other
ages did not show an effect. The small quantity of studies, differences between these studies, and their low quality rating, suggest caution in interpreting these results.

**Objective 4**

**DENTAL FLUOROSIS**

Dental fluorosis was the most widely and frequently studied of all negative effects. The fluorosis studies were largely cross-sectional designs, with only four before-after designs. Although 88 studies of fluorosis were included, they were of low quality. The mean validity score for fluorosis was only 2.8 out of 8. All, but one, of the studies were of evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for the effects of potential confounding factors, or reducing potential observer bias were uncommon.

As there may be some debate about the significance of a fluorosis score at the lowest level of each index being used to define a person as ‘fluorosed’, a second method of determining the proportion ‘fluorosed’ was selected. This method describes the number of children having dental fluorosis that may cause ‘aesthetic concern’.

With both methods of identifying the prevalence of fluorosis, a significant dose-response relationship was identified through a regression analysis. The prevalence of fluorosis at a water fluoride level of 1.0 ppm was estimated to be 48% (95% CI 40 to 57) and for fluorosis of aesthetic concern it was predicted to be 12.5% (95% CI 7.0 to 21.5). A very rough estimate of the number of people who would have to be exposed to water fluoride levels of 1.0 ppm for one additional person to develop fluorosis of any level is 6 (95% CI 4 to 21), when compared with a theoretical low fluoride level of 0.4 ppm. Of these approximately one quarter will have fluorosis of aesthetic concern, but the precision of these rough estimates is low. These estimates only apply to the comparison of 1.0 ppm to 0.4 ppm, and would be different if other levels were compared.

**BONE FRACTURE AND BONE DEVELOPMENT PROBLEMS**

There were 29 studies included on the association between bone fracture and bone development problems and water fluoridation. Other than fluorosis, bone effects (not including bone cancers) were the most studied potential adverse effect. These studies had a mean validity score of 3.4 out of 8. All but one study were of evidence level C. These studies included both cohort and ecological designs, some of which included analyses controlling for potential confounding factors. Observer bias could potentially play a role in bone fracture studies, depending on how the study is conducted.

The evidence on bone fracture can be classified into hip fracture and other sites because there are more studies on hip fracture than any other site. Using a qualitative method of analysis (Figure 8.1), there is no clear association of hip fracture with water fluoridation. The evidence on other fractures is similar. Overall, the findings of studies of bone fracture effects showed small variations around the ‘no effect’ mark. A meta-regression of bone fracture studies also found no association with water fluoridation.

**CANCER STUDIES**

There were 26 studies of the association of water fluoridation and cancer included. Eighteen of these studies are from the lowest level of evidence (level C) with the highest risk of bias.

There is no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers. Only two studies considered thyroid cancer and neither found a statistically significant association with water fluoridation.

Overall, no clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer or all cancers was found.

**OTHER POSSIBLE NEGATIVE EFFECTS**

A total of 33 studies of the association of water fluoridation with other possible negative effects were included in the review. Interpreting the results of studies of other possible negative effects is very difficult because of the small numbers of studies that met inclusion criteria on each specific outcome,
and poor study quality. A major weakness of these studies generally was failure to control for any confounding factors.

Overall, the studies examining other possible negative effects provide insufficient evidence on any particular outcome to permit confident conclusions. Further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

**Objective 5:**

The assessment of natural versus artificial water fluoridation effects is greatly limited due to the lack of studies making this comparison. Very few studies included both natural and artificially fluoridated areas, and direct comparisons were not possible for most outcomes. No major differences were apparent in this review, however, the evidence is not adequate to make a conclusion regarding this objective.

**Conclusions**

This review presents a summary of the best available and most reliable evidence on the safety and efficacy of water fluoridation.

Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken. As such, this review should provide both researchers and commissioners of research with an overview of the methodological limitations of previous research conducted in this area.

The evidence of a benefit of a reduction in caries should be considered together with the increased prevalence of dental fluorosis. The research evidence is of insufficient quality to allow confident statements about other potential harms or whether there is an impact on social inequalities. This evidence on benefits and harms needs to be considered along with the ethical, environmental, ecological, costs and legal issues that surround any decisions about water fluoridation. All of these issues fell outside the scope of this review.

Any future research into the safety and efficacy of water fluoridation should be carried out with appropriate methodology to improve the quality of the existing evidence base.
1. BACKGROUND

This review has been commissioned by the Chief Medical Officer of the Department of Health to ‘carry out an up to date expert scientific review of fluoride and health’ (Paragraph 9.20, Our Healthier Nation). The original objective given to the review team by the Department of Health was to conduct a systematic review of the efficacy and safety of water fluoridation. The protocol, including specific objectives, was then written by the review team, with the consultation and agreement of the advisory panel and in discussion with the Department of Health. The review agreed upon was a review of human epidemiological studies of water fluoridation.

The impact of fluoridation of drinking water supplies depends on a number of major issues: the potential benefits (including improved dental health and reductions in dental health inequalities); the potential benefits over and above that offered by the use of alternative interventions and strategies (e.g. fluoridated toothpaste); and the potential harms (including dental fluorosis, bone fractures and bone development problems, genetic mutations, birth defects, cancer and hypersensitivity).

This study aims to provide a systematic review of the best available evidence on potential positive and negative effects in order to assess the effects of water fluoridation. Decisions on artificial water fluoridation of course need to examine ethical issues, environmental and ecological impacts, cost and legal issues. These considerations are outside the scope of this review.

Systematic reviews locate, appraise and synthesise evidence from scientific studies in order to provide informative empirical answers to scientific research questions. They are therefore valuable sources of information for decision-makers. Systematic reviews differ from other types of review in that they adhere to a strict scientific design with the aims of making them more comprehensive, minimising the chance of bias and improving reliability. The intention is that a systematic review, rather than reflecting the views of authors or being based on only (a possibly biased) selection of the published literature, will contain a comprehensive assessment and summary of the available evidence. (For further information on systematic review methodology, see NHS Centre for Reviews and Dissemination Report 4 1996 and Sutton 1998.)

The history of health technology development shows that there have been numerous new interventions that were promising (or harmful) in animal and laboratory studies that turned out to be ineffective (or safe) when tested in humans. One example would be the drug omeprazole (Losec®) which caused gastric tumours in pre-clinical animal studies. However, such tumours have not been documented in humans, even in patients with conditions that require continuous treatment for many years. In general, when human data are available, animal or laboratory data provide far less reliable estimates of effect and, as such, do not bear significant weight on decisions about interventions. Such data will not be considered in this review.

A variety of study designs can be used to assess the effectiveness of a population-based intervention such as water fluoridation. These range from simple descriptive studies (e.g. cross-sectional), to studies of correlation at the population level (e.g. ecological studies), to studies of individual-based associations (e.g. case-control, before-after, and cohort studies) to formal experiments (e.g. randomised controlled trials).

The randomised controlled trial randomising individuals to fluoridated or non-fluoridated water would be the gold standard. However, studying the effects of water fluoridation poses problems for the use of the randomised controlled trial design. Water fluoridation affects population groups and it is thus difficult to randomly assign individuals to receive either fluoridated or non-fluoridated water. An alternative would be to randomise communities to fluoridated or non-fluoridated water. The fact that whole populations are either exposed or not exposed also poses a problem for cohort and case-control studies. Comparing exposures and outcomes between different population groups may cause problems as the two populations may differ with respect to other exposures or characteristics and so a causal relationship between the observed exposure and outcomes cannot be assumed. In observational studies (e.g. other than a randomised controlled trial) many people know whether or not a water supply is fluoridated and so blinding would not be possible, thus risking bias in observations.
Some possible adverse effects of water fluoridation may take many years to develop and so unless a study is specifically designed to investigate the relationship of these outcomes to fluoridation the relationship may go undetected. An assessment of the effectiveness of fluoridation on the incidence of caries is difficult because there are a number of factors that may influence caries prevalence other than fluoride in water, and these have changed over time. These factors include the introduction of fluoridated toothpaste, mouth rinses and improved dental hygiene in general. Traditional reviews of the literature tend to ignore the variable quality of studies and are therefore unlikely to present a reliable summary. Ideally, systematic reviews concentrate on studies that provide the strongest evidence, but where only a few good studies are available weaker designs may have to be considered.

Existing reviews do not address the major issues of benefit and harm in conjunction and in a systematic manner, as this review aims to do. The explicit methods used in this systematic review will limit bias through the use of specific inclusion criteria, and a formal assessment of the quality and reliability of the studies reviewed. The use of meta-analysis will increase statistical power and thus the precision of estimates of treatment effects and exposure risks. Finally, this review attempts to generate new questions and identify gaps in the research evidence.

1.1 Purpose

The aim of this systematic review is to assess the evidence on the positive and negative effects of population-wide drinking water fluoridation strategies to prevent caries. To achieve this aim five objectives have been identified:

Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

Objective 2: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Objective 3: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?

Objective 4: Does water fluoridation have negative effects?

Objective 5: Are there differences in the effects of natural and artificial water fluoridation?
2. METHODS

A diagram illustrating the stages of this systematic review's methods is presented in Figure 2.1.

2.1 Search strategy

2.1.1 Preliminary search

A preliminary search was undertaken to provide information on available reviews of fluoridation and to estimate the potential size of the research evidence on the effects of fluoride supplementation of drinking water. The preliminary search was carried out in several stages:

- Identification and collection of reviews of fluoridation.
- Medline search using a methodology filter strategy to identify the scope of the systematic reviews and meta-analyses literature (date range 1966 - 03/1999).
- Medline and Embase searches using a methodology filter strategy to identify primary studies including any randomised trials. (Medline date range 1966 - 05/1999; Embase date range 1980 – 05/1999).

The Medline and Embase databases were both searched using WinSpirs/SilverPlatter software. Further details about the preliminary search process are given in Appendix B, Section 1. The preliminary search strategy to retrieve systematic review and meta-analyses literature is included in Appendix B, Section 3.

2.1.2 Electronic database search

The full search built on the preliminary search strategies and involved searching a wide range of medical, political and environmental/scientific databases to identify primary studies. Each database was searched from its starting date to June/October 1999 (due to the number of databases, searches were carried out over a four month period). A list of the databases searched at each stage of the review and the dates searched are given in Appendix B, Section 2. Full details of all the strategies used in this review are given in Appendix B, Section 4. The databases searched were as follows:

- Medline
- Embase
- NTIS (National Technical Information Service)
- Biosis
- Current Contents Search (Science Citation Index and Social Science Citation Index)
- Healthstar (Health Service Technology, Administration and Research)
- HSRProj
- TOXLINE
- Chemical Abstracts
- OldMedline
- CAB Health
- FSTA (Food Science and Technology Abstracts)
- JICST- E Plus (Japanese Science and Technology)
- Pascal
- EI Compendex (Engineering Index)
- Environline
- PAIS (Public Affairs Information Services)
- SIGLE (System for Information on Grey Literature in Europe)
- Conference Papers Index
- Water Resources Abstracts
- Agricola (Agricultural Online Access)
- Waternet
- AMED (Allied and Complementary Medicine Database)
- Psyclit
- LILACS (Latin American and Caribbean Health Sciences Literature)
All references identified by search methods and submissions
n = 3246

Relevance Criteria
1. Relates directly to fluoride in drinking water supplies
2. Is a primary study (not a review of studies)
3. Research involves only humans
4. Involves two groups with different fluoride concentrations in water supply
5. For caries studies: evaluates two points in time, one of which is less than one year since the change of water fluoridation status in one of the groups

Inclusion Criteria (set 1)
Studies measuring possible positive effects (i.e. caries)
1. At least two populations compared
2. Different fluoride levels in different populations
3. Prospective study design, assessing two points in time
4. Start of study less than one year since change in fluoridation status
5. Measurable outcomes reported (i.e. Decayed, Missing and Filled Teeth score)

Inclusion Criteria (set 2)
Studies measuring possible negative effects (i.e. cancer, fluorosis, etc)
1. At least two populations compared
2. Different fluoride levels in different populations

Data extraction
Analysis
REPORT

Figure 2.1 Review methods
2.1.3 Other searching
The World Wide Web was searched for web pages maintained by others interested in the issue of water fluoridation. A web page was designed and maintained by the NHS Centre for Reviews and Dissemination, University of York to inform the public on the purpose, methods and progress of the review. The website included an e-mail response to enable members of the public and other organisations to submit articles for consideration. In addition to numerous individuals, examples of organisations that submitted lists of references are the National Pure Water Association and the British Fluoridation Society. Furthermore, advisory board members were asked to submit references or reports.

2.1.4 Hand searches
Hand searching of Index Medicus and Excerpta Medica was undertaken. Index Medicus was searched from 1959 back to 1945; Excerpta Medica was searched from 1973 back to 1955. A further sample of studies published before 1945 was retrieved from Index Medicus and Excerpta Medica and established that further searching was not required. Appendix B, Section 3 provides a list of search terms used in this hand searching process. The bibliographies of the eligible papers were also hand searched. Attempts were made to contact authors for further information if necessary. Further information about studies done in the UK was sought and obtained through the Public Records Office.

2.1.5 Updating the search
Update searches were undertaken at the beginning of February 2000. In order to identify the most useful databases, the included studies were examined to determine which of the above resources yielded the most studies included. Medline, Embase, Toxline and the Current Contents (Science Citation Index) were identified in this manner and included in the update search process.

2.1.6 Management of references
As such a wide range of databases had been searched, some degree of duplication of references resulted. In order to manage this issue, the titles and abstracts of the bibliographic records retrieved were downloaded and imported into Endnote (ISI ReSearch Soft, USA) reference management software to remove duplicate records.

2.2 Inclusion criteria

2.2.1 Methodological and quality criteria
Groups exposed or not exposed to fluoride may differ in respect to factors other than fluoride exposure itself. Some of these differences may be related to the outcomes under investigation (level of tooth decay, dental fluorosis, fractures etc) and so will confound any observed relationship and thus should be controlled for in the analysis. Confounding factors are factors that can cause or prevent the outcome of interest. In the case of water fluoridation these are likely to include age, gender, ethnicity, other sources of fluoridation and social class. Factors likely to modify the effect of fluoride on the outcomes under investigation, such as the level of tooth decay or delayed tooth eruption in the population before the introduction of fluoridation should also be considered.

Another important factor to be taken into account in assessing the effects of water fluoridation is blinding of outcome assessment. Blinding should be used to protect against the possibility that knowledge of participant’s exposure to water fluoridation may affect the ways in which the investigators assess outcomes. Knowledge of outcomes may also affect assessment of fluoridation status and other factors in retrospective studies.

The following methodological issues were considered when assessing studies for inclusion: selection, confounding, and measurement. Study designs are often graded hierarchically according to their quality, or degree to which they are susceptible to bias. The hierarchy indicates which studies should be given most weight in a synthesis. In this review, the degree to which each study dealt with the methodological issues was graded into three levels of evidence:
LEVEL A (HIGHEST QUALITY OF EVIDENCE, MINIMAL RISK OF BIAS)

- Prospective studies that started within one year of either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least five years for negative effects.
- Studies either randomised or address at least three possible confounding factors and adjust for these in the analysis where appropriate.
- Studies where fluoridation status of participants is unknown to those assessing outcomes.

LEVEL B (EVIDENCE OF MODERATE QUALITY, MODERATE RISK OF BIAS)

- Studies that started within three years of the initiation or discontinuation of water fluoridation, with a prospective follow up for outcomes.
- Studies that measured and adjusted for less than three but at least one confounding factor.
- Studies in which fluoridation status of participants was known to those assessing primary outcomes, but other provisions were made to prevent measurement bias.

LEVEL C (LOWEST QUALITY OF EVIDENCE, HIGH RISK OF BIAS)

- Studies of other designs (e.g. cross-sectional), prospective or retrospective, using concurrent or historical controls, that meet other inclusion criteria.
- Studies that failed to adjust for confounding factors.
- Studies that did not prevent measurement bias.

Studies meeting two of the three criteria for a given evidence level were assigned the next level down. For example, if a study met the criteria for prospective design and blinding for level A, but was neither randomised nor controlled for three or more potential confounding factors, it was assigned level B. Evidence rated below level B was not considered in our assessment of positive effects. However, this restricted assessment of the evidence for Objective 3, so the best level of evidence relevant to this objective (from any study design) was included. In our assessment of possible negative effects, all levels of evidence were considered. Adjustment for confounding factors required analysis of data, simply stating that two study groups were similar on noted confounding factors was not considered adequate.

2.2.2 Objective specific criteria

Specific inclusion criteria for each objective were based on the participants, intervention, outcomes measured and overall design of the study. All criteria were defined before the studies were assessed and were based on criteria commonly applied when critically appraising community based interventions (Elwood 1998). This review is limited to studies investigating the effects of water fluoridation on human populations. The objective-specific criteria for inclusion based on study design were:

OBJECTIVE 1. DOES FLUORIDATION OF DRINKING WATER SUPPLIES PREVENT CARIES?

Participants:
- Populations receiving fluoridated water (naturally or artificially)
- Populations receiving non-fluoridated water

Intervention:
- A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.

Outcomes:
- Any measure of dental decay

Study designs:
- Prospective studies comparing at least two populations, one receiving fluoridated the other non-fluoridated water, with at least two points in time evaluated.
**OBJECTIVE 2. IF FLUORIDATION IS SHOWN TO HAVE BENEFICIAL EFFECTS, WHAT IS THE EFFECT OVER AND ABOVE THAT OFFERED BY THE USE OF ALTERNATIVE INTERVENTIONS AND STRATEGIES?**

*Participants:*
- Populations receiving fluoridated water (naturally or artificially) in addition to other interventions.
- Populations receiving non-fluoridated water in addition to other interventions.

*Intervention:*
- A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.

*Outcomes:*
- Any measure of dental decay.

*Study designs:*
- Prospective studies comparing at least two populations, to investigate the differences in levels of tooth decay between the populations in the presence of other sources of fluoride, e.g. fluoridated toothpaste. Where specific information on the use of other sources of fluoride is not supplied, populations in studies conducted after 1975 in industrialised countries were assumed to have been exposed to fluoridated toothpaste.

**OBJECTIVE 3. DOES FLUORIDATION RESULT IN A REDUCTION OF CARIES ACROSS SOCIAL GROUPS AND BETWEEN GEOGRAPHICAL LOCATIONS?**

*Participants:*
- Populations from different social groups and geographic locations receiving fluoridated water (naturally or artificially).
- Populations from different social groups and geographic locations receiving non-fluoridated water.

*Intervention:*
- Fluoride at any concentration present in drinking water, either controlled or naturally occurring

*Outcomes:*
- Any measure of dental decay.

*Study designs:*
- Any study design comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations.

**OBJECTIVE 4. DOES FLUORIDATION HAVE NEGATIVE EFFECTS?**

*Participants:*
- Populations receiving fluoridated water (either naturally or artificially).
- Populations receiving non-fluoridated water.

*Intervention:*
- Fluoride at any concentration present in the water supply, either naturally occurring or artificially added.

*Outcomes:*
- Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other possible negative effects reported in the literature.

*Study designs:*
- Any study design comparing the incidence of any possible adverse effect between two populations, one with fluoridated water and the other with non-fluoridated water.

**OBJECTIVE 5. ARE THERE DIFFERENTIAL EFFECTS OF NATURAL AND ARTIFICIAL FLUORIDATION?**

*Participants:*
- Populations receiving artificially fluoridated water.
- Populations receiving naturally fluoridated water.
• Populations receiving non-fluoridated water.

**Intervention:**
• Fluoride at any concentration from a naturally or an artificially fluoridated water source.

**Outcomes:**
• Possible positive effects: Any measure of dental decay.
• Possible negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other possible negative effects reported in the literature.

**Study designs:**
• Any study design comparing populations exposed to different water fluoride concentrations, results obtained from areas using artificially and naturally fluoridated water supplies were compared to investigate any differences in effect.

Studies meeting the above objective specific criteria for inclusion were also assigned a level of evidence, as described above.

### 2.3 Assessment of papers for inclusion

#### 2.3.1 Relevance assessment

Three reviewers independently assessed each title and abstract located through the searches for relevance to the review. Decisions about the inclusion of studies were made according to the following pre-determined criteria:

• Relates directly to fluoride in drinking water supplies.
• Is a primary study (not a review of studies).
• Research involves humans.
• Involves two groups with different fluoride concentrations in water supply.
• For caries studies: evaluates two points in time, one of which is less than three years since the change of water fluoridation status in one of the two groups.

Full articles of titles and abstracts found to be relevant to the review were obtained for full assessment of inclusion criteria.

#### 2.3.2 Assessment of papers for inclusion criteria

Three reviewers independently assessed each paper for the pre-determined inclusion criteria, as stated above. Inclusion criteria were assessed for each of the objectives separately. Disagreements were resolved through consensus.

### 2.4 Data extraction

Extraction of data from individual included studies was independently performed by two reviewers, and checked by a third reviewer. Disagreements were resolved through consensus. Papers in languages other than English were assessed for inclusion criteria and data extracted using appropriate translators. Languages translated were Bulgarian, Chinese, Czech, Dutch, French, German, Greek, Hungarian, Italian, Portuguese, Russian and Spanish. Data were extracted into an MS Access database (Microsoft Corporation 1989-96). Tables showing baseline information and results were produced for each study and are presented in Appendix C.

### 2.5 Assessment of study validity

Study validity was formally assessed using validity checklists based on the checklist in NHS Centre for Reviews and Dissemination Report Number 4 (NHS CRD, 1996). The checklist was modified to address issues of water fluoridation. Separate checklists were devised for studies using a case-control design and all other study designs combined. These checklists are presented in Appendix D. Each study was assigned a ‘level of evidence’ using the definitions given above, and a validity score, based on the number of checks achieved on the checklist. The maximum score was 8 for all study designs except case control studies which had a total of 9 possible points. Study validity was assessed independently by two reviewers, with disagreements resolved through consensus.
The level of evidence (A, B, or C) is generic, and was used to classify studies for inclusion criteria based on overall quality and chance for bias. The validity assessment checklist is more specific to water fluoridation studies. Therefore, the validity checklist assessment is stricter.

2.6 Data analysis

Where the data were in a suitable format, measures of effect (with their 95% confidence intervals) for the major outcomes identified were shown on forest plots. This allowed a visual evaluation of the overall data set. The range of measures of effect for each outcome is also presented in the text.

Differences among studies may explain why individual studies report differing estimates of effect. These differences may relate to study design, geographic location, age of participants, type and duration of intervention, and methods of outcome assessment. Such differences between studies are known as heterogeneity, which may or may not be important. Some heterogeneity can be expected to occur by chance. A distinction is sometimes made between statistical heterogeneity (differences in the reported effects), methodological heterogeneity (differences in study design) and clinical heterogeneity (differences between studies in key characteristics of the participants, interventions or outcome measures). Statistical tests for heterogeneity are used to assess whether the observed variability in study results (measures of effect) is greater than that expected to occur by chance. If there is statistically significant heterogeneity between the estimates derived from different studies, this may result in a decision not to combine the studies in a meta-analysis. Statistical heterogeneity can exist even when all the studies included show an effect in the same direction (e.g. a protective effect), but there is variation in the estimate of the magnitude of the effect. Heterogeneity was investigated by visual examination of the forest plots and statistically using the Q-statistic. Even if the assessment of heterogeneity is not statistically significant there may be important heterogeneity.

Where no evidence of statistically significant heterogeneity was found, a meta-analysis was conducted to produce a pooled estimate of the measure of effect. The DerSimonian and Laird random effects model, which assumes that the study specific measures of effect come from a random distribution of measures of effect with a fixed mean and variance, was used to combine studies. It is a more conservative analysis, resulting in broader confidence intervals, used because some degree of underlying heterogeneity among the studies was assumed.

Tables indicating the general effect of fluoridation found in each study were created for each item, and, where possible, the point estimate and a measure of statistical significance (using the 95% confidence interval or p-value) of the finding was also included. Validity scores were included in these tables to allow assessment of the relationship between study quality and strengths of the association with fluoridation. Statistical analysis was carried out using StatsDirect (CamCode, England), Stata (Stata Corporation, USA), SAS (SAS institute Inc., USA) and Access (Microsoft Corporation, USA).

A table was not made for dental fluorosis, as the method of analysis used for this outcome differed from that used for other outcomes. The analysis used for fluorosis compared each fluoridated study area to each non-fluoridated study area, using a regression analysis, rather than comparing the differences found within each study to the differences found within other studies.

Where possible, meta-regression was used to investigate and explain sources of heterogeneity among studies. Meta-regression is an exploratory statistical analytical technique, which investigates the importance and nature of relationships between study results and study characteristics, and can be used to explore sources of heterogeneity. This is a modelling exercise that estimates the amount by which each identified ‘predictor variable’ (e.g. age) reduces the remaining heterogeneity. Dental caries and bone fracture results were analysed using meta-regression in order to assess the impact of potential sources of heterogeneity and estimate the underlying effect of water fluoridation. Meta-regression was carried out using Stata v. 6.0 (Stata Corporation, USA). The heterogeneity among fluorosis studies was explored by including variables that may account for the observed heterogeneity in the regression model.

Publication bias is defined as the failure to publish research on the basis of the nature and directional significance of the results. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. The data provided by the studies included in this review were not in a suitable format to allow investigation of publication bias using standard procedures (e.g. Funnel plots), and so a narrative approach was used to discuss publication bias.
3. GENERAL RESULTS

3.1 General results

The search identified over 3200 papers, of which 734 met relevance criteria. Upon closer inspection, 254 of these met full inclusion criteria for one or more of the objectives; these 254 papers relate to 214 studies (some papers refer to the same study). Among these there were 26 studies relevant to Objective 1, the effect of water fluoridation on dental caries; 9 of these also met inclusion criteria for Objective 2. For Objective 3, 13 studies were included. For Objective 4, a total of 176 studies were included. There were 88 studies on dental fluorosis, 29 on bone fractures, 26 on cancer, and 33 studying other possible adverse effects. These included studies came from 30 countries, were published in 14 languages and ranged in publication dates from 1939 to 2000. No randomised controlled trials of the effects of water fluoridation were found. The study designs used included 45 ‘before and after’ studies, 102 cross-sectional studies, 47 ecological studies, 13 cohort (prospective or retrospective) studies and seven case-control studies. Several studies were reported in multiple papers over a number of years. For example, the original studies from Michigan were published in six papers, between 1942 and 1962.

3.2 Validity assessment

None of the included studies were of evidence level A. The reason for this among the studies evaluating dental caries was that none addressed three or more confounding factors. For Objectives 1 and 2, all studies that met inclusion criteria were evidence level B. All but three of the studies assessing Objective 3, were evidence level C, the others were evidence level B. Among the studies of possible adverse effects of water fluoridation, Objective 4, the majority were found to be level C evidence because they lacked a prospective, longitudinal design. Studies used to compare the effects of natural versus artificial water fluoridation, Objective 5, were evidence level B for possible positive effects and mainly level C for possible negative effects. The validity checklist scores and level of evidence are presented in D.

3.3 Extracted data

Data extracted from all of the included studies are presented in tables in Appendix C. Each outcome is presented in two separate tables, the first listing baseline data about the groups being studied, such as location and year of study, gender, and the methods used to assess outcome. The second table presents the results of each study by each outcome.

3.4 Protocol changes

Changes to the original protocol were minimal. The wording of the objective specific inclusion criteria was altered to clarify the intent of the criteria. The range of analyses undertaken was broader than had been described in the protocol. Due to extremely limited evidence, the inclusion criteria for Objective 3 were expanded to include studies of level C evidence, and limited to studies from the UK. These changes were made with the consultation of and agreement from the advisory panel. Full details of changes are included in Appendix M.
What are the effects of fluoridation of drinking water supplies on the incidence of caries?

A total of 26 studies of the effect of water fluoridation on dental caries were found, reported in 73 articles published between 1951 and 2000. Five unpublished studies were located (Hobbs 1994, Wragg 1992, Gray 1999, Holdcroft 1999 and Gray, 2000). The before-after study design was used in all but three of the included studies. The three exceptions were two prospective cohort studies (Hardwick 1982, Maupomé 2000) of caries in children and one retrospective cohort study (Pot 1974) of adults with false teeth. An example of the before-after design is a study in which two groups of 12-year olds from two similar populations were examined for prevalence of caries prior to initiating water fluoridation in one of the groups. Five years after starting water fluoridation, 12 year olds were examined in the two areas (one fluoridated, the other not). The rates of caries in the first groups were then compared with the rates in the second groups. It is important to note that the children are different in the before and after periods. All before-after studies identified by the search met the inclusion criteria. Three of the studies met inclusion criteria but were not included in the main analysis and are discussed in section 4.3 (Klein 1946, Holdcroft 1999 and Gray 2000). The Hardwick cohort study examined two groups of British children at age 12 prior to the initiation of fluoridation in the water supply of one group, and followed these same children with annual examinations for four years.

Seven studies assessed the effect of discontinuing water fluoridation, including seven before-after analyses and one cohort study (Attwood 1988, Hobbs 1994, Kalsbeek 1993, Kunzel 1997, Maupomé 2000, Seppa 1998 and Wragg 1992). The Maupomé cohort study examined two groups of 8 and 14 year-old children within 14 to 19 months after fluoridation was stopped in one area and continued in the other. These same children were then re-examined three years later. This study also included a second group of children 8 and 14 years old at the follow-up examination, and so is both a before-after and cohort design. Only one of the 26 studies included examined adults (Pot 1974).

The studies assessing efficacy of water fluoridation all achieved evidence level B, and an average checklist score of 5 out of 8 (range 3.5 to 6.8). The checklist items most commonly missed by these studies were blinding of the examiners assessing outcomes to the children’s exposure status, reliable measurement (or adequate reporting) of the fluoride concentration, and adequate investigation of confounding factors. None attempted to control for confounders using multivariate analysis (a technique commonly used since the early 1980s). The only method used to address confounding was by presenting data stratified by age or gender. Many additional studies were excluded because they failed to include a baseline examination prior to starting or stopping water fluoridation.

The measure of effect measure used in the main analysis was the difference of the change in caries from the baseline to the final examination in the fluoridated compared with the control area (Appendix E). For example, the change in DMFT in the fluoridated area (final survey minus baseline survey) minus the change in DMFT in the control (non-fluoridated) area (final survey minus baseline survey) is the difference in the change in DMFT for that study. The two main outcomes investigated by studies estimating the effect of fluoridation on caries were DMFT (and dmft) score and the proportion of caries-free children (in both primary and secondary dentition).

Tables 4.1 - 4.5 show the 26 studies that have been included in assessing objective 1. In these tables, the mean difference of the change in caries measurement between the fluoride and control areas is shown. If the reduction in dental caries between pre- and post-fluoridation periods was greater in the fluoridated group than in the non-fluoridated group the mean difference will be greater than zero. Thus, a mean difference greater than zero indicates a benefit of water fluoridation and a mean difference less than zero indicates no benefit of water fluoridation. If the 95% confidence intervals include zero the difference is not statistically significant at the 5% level.
4.1 Studies in which fluoridation was initiated

Figure 4.1 shows the mean difference of the change in the proportion (\%) of caries-free children in the exposed (fluoride) group compared with the control group (low fluoride), for all ages extracted (colour coded by age), for studies in which fluoridation was initiated after the baseline survey.

Figure 4.1: Increase in proportion (\%) of caries-free children in fluoridated compared to non-fluoridated areas (mean difference and 95% CI)
The vertical line, at 0, is the 'no effect' line for measures of difference. Studies are indicated with a rectangle showing the 95% confidence intervals around the mean. The 95% confidence interval is the interval within which 95% of values of estimates derived from identified studies will fall. The rectangles are colour coded by age. If the rectangle crosses the 'no effect' line the difference is not statistically significant. If the rectangle is entirely to the right of the line the difference is statistically significant and fluoridation is associated with an increase in the proportion of children who are caries-free. If the rectangle is entirely to the left of the line the difference is statistically significant and fluoridation is associated with a decrease in the proportion of children who are caries-free.

The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.8% (interquartile range 5.05, 22.1%). There was a statistically significant change, with a greater proportion of caries-free children in the fluoridated area, in 19 analyses. One analysis found a statistically significant greater decrease in the proportion of caries-free children exposed to fluoridated water compared with those exposed to non-fluoridated water. The remaining 10 analyses were unable to detect a statistically significant difference. It is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9).

Figure 4.2 shows the mean difference of the change in dmft/DMFT in the exposed (fluoride) compared with the control group (low fluoride), separately by age (colour coded) for the four studies reporting dmft/DMFT, with 95% CIs.

Fifteen studies found a statistically significantly greater mean change in dmft/DMFT scores in the fluoridated areas than the non-fluoridated areas. The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth).

![Figure 4.2: Change in dmft/DMFT Score (mean difference and 95% CI)](image-url)
The Hardwick cohort study was plotted separately (figure 4.3) because the outcome measurements (increment in DMFT and DMFS) were too dissimilar to the others. In this study the effect of water fluoridation was assessed in the same children over a three-year period. This study showed a statistically significant mean difference in the increment in DMFT/DMFS score, with children in the fluoridated area having fewer new decayed, missing or filled teeth (or surfaces) after the three-year period. The examiners in this study were blind to the fluoridation status of the children.

Table 4.1 Mean difference of the change in the proportion of (%) caries-free children between the fluoride and control areas

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Teeth Type</th>
<th>Mean Difference (95% CI)</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunzel (1997)</td>
<td>5</td>
<td>Primary</td>
<td>9.4 (0.9, 17.9)</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>41.1 (36.0, 46.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Primary</td>
<td>19.4 (15.9, 22.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>25.2 (21.1, 29.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>9.5 (6.3, 12.7)</td>
<td></td>
</tr>
<tr>
<td>Beal (1981)</td>
<td>5</td>
<td>Primary</td>
<td>16.0 (3.2, 28.8)</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>19.0 (4.8, 33.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Primary</td>
<td>6.0 (-3.4, 15.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>-5.0 (-15.0, 5.0)</td>
<td></td>
</tr>
<tr>
<td>DHSS (1969)</td>
<td>5</td>
<td>Primary</td>
<td>17.0 (2.1, 31.9)</td>
<td>5.5</td>
</tr>
<tr>
<td>England</td>
<td>8</td>
<td>Not stated</td>
<td>18.0 (0.7, 35.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Not stated</td>
<td>8.0 (-1.2, 17.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Permanent</td>
<td>5.0 (-4.4, 14.4)</td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>5</td>
<td>Primary</td>
<td>14.0 (3.5, 24.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Not stated</td>
<td>9.0 (1.2, 16.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Permanent</td>
<td>3.0 (-2.9, 8.9)</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>5</td>
<td>Primary</td>
<td>14.6 (4.7, 24.4)</td>
<td></td>
</tr>
<tr>
<td>Adriasola (1959)</td>
<td>5</td>
<td>Primary</td>
<td>5.1 (-1.9, 12.1)</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Not stated</td>
<td>5.0 (0.1, 9.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Not stated</td>
<td>-4.9 (-8.3, -1.5)</td>
<td></td>
</tr>
<tr>
<td>Guo (1984)</td>
<td>5</td>
<td>Primary</td>
<td>-2.0 (-6.4, 2.4)</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>64.1 (55.4, 72.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Primary</td>
<td>0.4 (-4.8, 5.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>-28.5 (20.5, 36.5)</td>
<td></td>
</tr>
<tr>
<td>Beal (1971)</td>
<td>5</td>
<td>Not stated</td>
<td>2.0 (-8.0, 16.0)</td>
<td>4.8</td>
</tr>
<tr>
<td>Ast (1951)</td>
<td>5</td>
<td>Primary</td>
<td>22.1 (10.9, 33.3)</td>
<td>4.5</td>
</tr>
<tr>
<td>Brown (1965)</td>
<td>9-11</td>
<td>Permanent</td>
<td>36.1 (30.5, 41.7)</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>12-14</td>
<td>Permanent</td>
<td>15.8 (11.8, 19.8)</td>
<td></td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>5</td>
<td>Primary</td>
<td>26.0 (19.4, 32.6)</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The associations that were found in the studies in which fluoridation was initiated are presented in Tables 4.1 and 4.2. Table 4.3 shows the results of studies using outcome measures other than the proportion of caries-free children or dmft/DMFT score. Some studies either did not provide data on the variance of the estimate of effect or the number of individuals studied. Further information was sought from the authors of these studies, however, only one author was contacted successfully.
Studies without variance data were not included in the plots or in the meta-regression. The reason for excluding data from further analysis is stated in the table.

Whilst in 27 of the 30 analyses the direction of association between water fluoridation and the change in the proportion of caries-free children was positive (fewer caries), in only 20 of these comparisons were the differences statistically significant. In three analyses the direction of association was negative (one in five-year-olds and two in 12 year-olds), but only one of these found a statistically significant effect (Table 4.1).

In all 31 analyses the direction of association of the dmft/DMFT scores with fluoridation status was positive. Standard error data were only available for 16 of these analyses, all but one of which showed a statically significant positive effect of fluoridation (Table 4.2).

### Table 4.2 Mean difference of the change in dmft/DMFT between the fluoride and control areas

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Teeth Type</th>
<th>Mean Difference (95% CI)</th>
<th>Included in Analysis</th>
<th>Reason not Included in Further Analysis</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunzel (1997)</td>
<td>5, 8, 8, 12, 15</td>
<td>Primary Primary Primary Permanent Permanent Permanent</td>
<td>0.6 (0.2, 1.0) 2.1 (1.8, 2.4) 1.3 (1.2, 1.4) 2.9 (2.6, 3.2) 3.7 (3.3, 4.1)</td>
<td>Yes</td>
<td></td>
<td>5.8</td>
</tr>
<tr>
<td>Beal (1981)</td>
<td>5, 8, 8, 12</td>
<td>Primary Primary Primary Permanent Permanent Permanent</td>
<td>1.7 (0.6, 2.8) 0.5 (0.1, 0.9) 1.2 (0.4, 2.0) 0.6 (-0.2, 1.4)</td>
<td>Yes</td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>DHSS (1969) England</td>
<td>5, 8, 12</td>
<td>Primary Primary Primary Permanent Permanent Permanent</td>
<td>1.6 0.8 1.0 1.5</td>
<td>No</td>
<td>No standard error data</td>
<td>5.5</td>
</tr>
<tr>
<td>Wales</td>
<td>5, 12, 14</td>
<td>Primary Primary Primary Permanent Permanent Permanent</td>
<td>2.1 2.5 2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loh (1996)</td>
<td>7-9, 7-9</td>
<td>Permanent Permanent</td>
<td>3.1 2.1</td>
<td>No</td>
<td>No standard error data</td>
<td>5.1</td>
</tr>
<tr>
<td>Guo (1984)</td>
<td>5, 8, 8, 12, 15</td>
<td>Primary Primary Primary Primary Permanent Permanent Permanent</td>
<td>3.6 (2.6, 4.6) 1.6 (1.4, 1.8) 4.4 (3.9, 4.9) 2.6 (2.2, 3.0) 3.8 (2.7, 4.9)</td>
<td>Yes</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Alvarez-Ubilla (1959)</td>
<td>5</td>
<td>Primary</td>
<td>2.2</td>
<td>No</td>
<td>No standard error data</td>
<td>4.5</td>
</tr>
<tr>
<td>Arnold (1956)</td>
<td>12, 15, 8</td>
<td>Permanent Permanent Permanent</td>
<td>1.2 3.1 1.2</td>
<td>No</td>
<td>No standard error data</td>
<td>4.5</td>
</tr>
<tr>
<td>Blayney (1960)</td>
<td>12, 8</td>
<td>Permanent Permanent</td>
<td>3.4 1.8</td>
<td>No</td>
<td>No standard error data</td>
<td>4.5</td>
</tr>
<tr>
<td>Brown (1965)</td>
<td>12, 14, 9-11</td>
<td>Permanent Permanent</td>
<td>4.1 (3.4, 4.8) 2.1 (1.7, 2.5)</td>
<td>Yes</td>
<td></td>
<td>4.5</td>
</tr>
</tbody>
</table>

The study with the highest validity score (Hardwick, 1982) showed a statistically significant difference in the increment in both DMFS and DMFT scores, with a lower increment in the fluoridated area compared with the control area. One study (Backer-Dirks, 1961) considered the average number of all dentinal lesions and the average number of approximal dental lesions. This study found the direction of association of fluoridation with caries to be positive (fewer caries) but no measure of the statistical significance of this effect was provided. Two studies (Beal, 1971 and Arnold, 1956) looked at deft score. Whilst both these studies found the direction of association to be positive, only one of these studies (Beal, 1971) provided standard error data. This study showed a statistically significant
positive effect of fluoridation. One study (Ast, 1951) compared the number of erupted teeth per child before and after fluoridation was initiated and found the direction of association to be positive with fluoridation (more erupted teeth per child) in 12 year-olds but negative in 8 year-olds. No measure of the statistical significance of this association was provided, however, and the difference was so small that is unlikely that there was a statistically significant difference in the number of erupted teeth in the fluoridated compared with the control area. This same study also looked at the DMFT rate per 100 erupted teeth and found the direction of association to be positive (greater decrease in the DMFT rate in the fluoridated area compared with the control area) with water fluoridation. However no measure of the significance of this association was provided. One study (Pot, 1974) found the proportion of adults with false teeth to be statistically significantly greater in the control (low-fluoride) area compared with the fluoridated area.

Table 4.3 Mean difference of the change in other caries measurements between the fluoride and control areas

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Mean Difference (95% CI)</th>
<th>Outcome</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardwick (1982)</td>
<td>12</td>
<td>2.5 (1.0, 3.9)</td>
<td>Increment in DMFS score</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.1 (0.4, 1.8)</td>
<td>Increment in DMFT score</td>
<td></td>
</tr>
<tr>
<td>Backer-Dirks (1961)</td>
<td>11-15</td>
<td>2.7</td>
<td>Average number of all approximal lesions</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>11-15</td>
<td>1.4</td>
<td>Average number of approximal dentinal lesions</td>
<td></td>
</tr>
<tr>
<td>Beal (1971)</td>
<td>5</td>
<td>2.5 (1.3-3.7)</td>
<td>deft score</td>
<td>4.8</td>
</tr>
<tr>
<td>Arnold (1956)</td>
<td>5</td>
<td>1.6</td>
<td>deft score</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ast (1951)</td>
<td>12</td>
<td>0.1</td>
<td>Number of erupted permanent teeth per child</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>-0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pot (1974)</td>
<td>5-55</td>
<td>11.2 (3.8, 18.6)</td>
<td>% with false teeth</td>
<td>4.0</td>
</tr>
</tbody>
</table>

4.2 Studies in which fluoridation was discontinued

Figure 4.4 shows the mean difference of the change in the dmft/DMFT and DMFS score in children in the exposed (fluoride) group compared with the control group (low fluoride), in studies in which fluoridation was discontinued after the baseline survey.

Wragg (1992)

Attwood (1988)

Kalsbeek (1993)

Seppa (1998) Age 9

Seppa (1998) Age 12

Seppa (1998) Age 15

Kalsbeek (1993)

![Figure 4.4: Stopping fluoridation: dmft/DMFT or DMFS score (mean difference and 95% CI)](image)

- dmft score
- DMFT score
- DMFS score
The range of measures of effect in dmft/DMFT scores (Figure 4.4) is –7.4 to –0.6. Two of the three studies using dmft/DMFT show a statistically significant difference: when fluoridation was discontinued there was a greater increase in caries in the fluoridated compared with the control area suggesting that fluoridation had been beneficial. The range in measures of effect for DMFS score was –18.8 to 0.2, with all but one of the studies suggesting that stopping water fluoridation had led to a greater increase in caries in the previously fluoridated area than in the non-fluoridated area. Only one of the four analyses using DMFS found a statistically significant difference. The three analyses that did not find a statistically significant effect all came from the same study (Seppa, 1998), but relate to different age groups (ages 9, 12 and 15 shown in ascending order of age on the graph).

Table 4.4 shows the results of the studies that examined the effects of stopping water fluoridation. In this table a positive difference indicates that the difference between the fluoridated and non-fluoridated areas in the caries outcome became greater after the cessation of water fluoridation. A negative difference shows that the difference narrowed when fluoridation stopped.

Table 4.4 Mean difference in caries outcome measures in studies in which fluoridation was discontinued

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Teeth Type</th>
<th>Mean Difference (95% CI)</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of caries-free children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunzel (1997)</td>
<td>8</td>
<td>Permanent</td>
<td>8.6 (-5.3, -2.5)</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHSS (1969)</td>
<td>5</td>
<td>Primary</td>
<td>-2.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Wragg (1992)</td>
<td>5</td>
<td>Primary</td>
<td>-21.6 (-37.1, -16.3)</td>
<td>4.5</td>
</tr>
<tr>
<td>Mean difference in dmft/DMFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunzel (1997)</td>
<td>12</td>
<td>Permanent</td>
<td>0.1 (-0.4, 0.3)</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalsbeek (1993)</td>
<td>15</td>
<td>Permanent</td>
<td>-7.4 (-8.5, -6.3)</td>
<td>5.5</td>
</tr>
<tr>
<td>DHSS (1969)</td>
<td>5</td>
<td>Primary</td>
<td>-16</td>
<td>5.5</td>
</tr>
<tr>
<td>Attwood (1988)</td>
<td>10</td>
<td>Permanent</td>
<td>-0.6 (-1.3, 0.1)</td>
<td>4.8</td>
</tr>
<tr>
<td>Hobbs (1994)</td>
<td>5</td>
<td>Primary</td>
<td>-1.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Wragg (1992)</td>
<td>5</td>
<td>Primary</td>
<td>-1.5 (-2.2, -0.7)</td>
<td>4.5</td>
</tr>
<tr>
<td>DMFS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seppa (1998)</td>
<td>6</td>
<td>Not stated</td>
<td>-0.1 (-0.5, 0.9)</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Permanent</td>
<td>-1.1 (-2.3, 0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>-0.9 (-4.2, 2.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>-18.8 (-21.3, -16.3)</td>
<td>5.5</td>
</tr>
<tr>
<td>Mean Difference in D1D2MFS* Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maupomé (2000)</td>
<td>8</td>
<td>Permanent</td>
<td>0.59 (0.41, 0.77)</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Permanent</td>
<td>1.39 (0.23, 2.55)</td>
<td></td>
</tr>
<tr>
<td>D1D2MFS* Incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maupomé (2000)</td>
<td>11</td>
<td>Permanent</td>
<td>0.13 (0.07, 0.34)</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Permanent</td>
<td>0.47 (0.02, 0.96)</td>
<td></td>
</tr>
</tbody>
</table>

*D1D2MFS is a modified DMFS score where D1 = an incipient lesion, D2 = a cavitated lesion

Of 22 analyses of stopping water fluoridation, 14 found the direction of association to be negative (that stopping water fluoridation led to an increase in caries in the previously fluoridated area compared to the never-fluoridated area). However only eight of these studies provided a measure of the significance of this association. Four of these analyses found that stopping water fluoridation had a statistically significant effect at the 5% level, while the other four did not. Eight analyses found the direction of association to be positive (that stopping fluoridation had not led to increases in caries in the previously fluoridated areas). Seven of these analyses (from Seppa 1998 and Maupomé 2000 of both before-after and cohort analyses), provided standard error data. Only the Maupomé before-after study found a statistically significant association, in both 8 and 14 year olds.
The Maupomé study also included a multiple regression on both the before-after and cohort data including age, sex, socio-economic status, site (still fluoridated or no longer fluoridated), use of snacks, swallowing of toothpaste, use of fluoride supplements and brushing/rinsing regime. For prevalence of D1D2MFS, higher age and lower socio-economic status were statistically significantly associated with caries prevalence. Higher scores were associated with the still-fluoridated site for the D1D2MFS score and D1 alone, but higher D2 alone scores were associated with the fluoridation ended site. For the cohort data, the regression analysis showed again that higher age and lower socio-economic status were associated with higher D1D2MFS scores. However, the association between score and site (still fluoridated or fluoridation ended) were less clear.

4.3 Studies which met inclusion criteria but were not included in the main analysis

Table 4.5 is a summary of the studies that met our inclusion criteria, but contained data in forms that could not be used in the pre-defined analysis. The data used in the reports by Holdcroft and Gray were derived from the British Association for the Study of Community Dentistry (BASCD) survey data. Each year the BASCD conducts an epidemiological survey of dental health in the UK. Every second year, 5-year-old children are examined in most regions of the UK (either a random sample or the whole population of a given health authority). These surveys are co-ordinated and published by the University of Dundee.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Reason</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein (1946)</td>
<td>Caries</td>
<td>Different caries measurement at baseline and final surveys</td>
<td>Author states that the findings of this report support a beneficial role of fluoride in caries prevention</td>
</tr>
<tr>
<td>Holdcroft (1999)</td>
<td>dmft</td>
<td>Results presented for 14 areas, no pairing of exposed and control areas so could not make direct comparisons</td>
<td>The conclusion of this study was that significant improvements in dmft levels is possible in non-fluoridated districts. When measured against fluoridated districts, it implies that the effectiveness of fluoridation is at least exaggerated. Efforts to improve dental health outside of the influence of drinking fluoridated water will impact changes in dmft level.</td>
</tr>
<tr>
<td>Gray (2000)</td>
<td>dmft</td>
<td>Results presented for 10 areas, 6 areas fluoridated, no pairing of exposed and control areas so could not make direct comparisons</td>
<td>After 10 years of fluoridation dental decay was lower in the fluoridated than in the low fluoride areas.</td>
</tr>
</tbody>
</table>

4.4 Studies with more than two study areas

The majority of studies assessing caries compared one fluoridated area to one non-fluoridated area. However, there were five studies with more than two study areas, such as two fluoridated areas compared with one non-fluoridated area. In the DHSS Welsh studies (DHSS 1969), data from Holyhead were excluded from the analysis because although Holyhead usually received fluoridated water, occasionally the water supply was supplemented from a non-fluoridated source.

For two studies (Gray 1999, Wragg 1992) the data from the two areas with the same fluoride level in their water supplies were combined as no differences between the study areas were discussed. In the Beal (1971) study, two of the study areas were similar in social class structure (one fluoridated and one non-fluoridated area) while the other fluoridated area had a higher proportion of immigrants and was poorer on the basis of a number of indicators than the other two. Therefore, this area was dropped from the analysis and only the two similar areas were included. The comparison of the lower social class area with the higher social class area is considered under Objective 3.

The fifth study with more than two areas was the Canadian study of the Brantford-Sarnia-Stratford areas (Brown 1965), which included a non-fluoridated area, an artificially fluoridated area, and a naturally fluoridated area. The non-fluoridated and artificially fluoridated areas were used for the analysis of Objective 1, while the comparison of artificial and naturally fluoridated areas is considered under Objective 5.
4.5 Possible confounding factors

There are a number of potential confounding factors in assessing the development of caries within studies. Age, gender, social class, ethnicity, country, tooth type (primary or permanent), mean daily regional temperature, use of fluoride, total fluoride consumption, method of measurement (clinical exam, radiographs, or both), and training of examiners are all possible confounding factors. While most studies described the age of participants, data on other potential confounders were rarely available. Another possibly important confounding factor is the number of erupted teeth per child. It has been suggested that fluoridation may delay the eruption of teeth and thus caries incidence could be delayed as teeth would be exposed to decay for a shorter period of time. Only one study compared the number of erupted teeth per child. The difference was very small and in opposite directions in the two age groups examined, however no measure of the statistical significance of these differences was provided. Only one of the studies attempted to control for confounding factors using multivariate analysis (Maupomé 2000).

4.6 Meta-regression

A meta-regression analysis was undertaken to investigate possible sources of heterogeneity between studies. Variables that may account for the differences in measures of effect seen among different studies (or in this case each different measure of effect included in the analysis) were included in the regression model. Variables included in the analysis relate to study design and patient characteristics. The analysis aims to investigate why there is a difference in the measure of effect calculated from each study rather than why caries prevalence differs between study areas within studies.

The outcome measure used for this analysis is different from that used in previous analyses. The outcome measure used is taken from only the final survey data and corresponds to the mean difference (MD) for the dmft/DMFT data and the risk difference (RD) for the proportion of caries free children data. The reason for using only data from the final survey was to allow investigation of the effect of baseline caries levels by including this as a variable in the meta-regression. If the mean difference of the change in caries incidence was used as the outcome measure (as it has for the earlier analyses) this may lead to a spurious association being found, due to the correlation between the outcome variable and the baseline caries variable.

A paired t-test was carried out to investigate whether there were any statistically significant differences between caries prevalence (as measured by the proportion of caries-free children or dmft/DMFT) in the two study areas at baseline for each study (Appendix J). No statistically significant differences were found (p= 0.97 for proportion caries-free children and p=0.77 for dmft/DMFT), and so the final outcome measures could be taken as measures of the effect of fluoridation on caries incidence. This also permitted the calculation of the mean proportion of caries free children or dmft/DMFT at baseline for each study, this variable was included in the regression analysis as an estimate of caries experience at baseline for each study comparison.

The analysis was carried out separately for the two main caries outcome measurements: the proportion (%) of caries-free children and dmft/DMFT. Data on possible sources of heterogeneity were extracted from the studies where possible. If not described in the paper, data on altitude and mean daily temperature were obtained from published sources.

The studies included in this analysis contribute more than one estimate to the meta-regression, although different children contribute to the different estimates within studies. It has been assumed in this analysis that these subgroups of people are independent, and hence each estimate has been treated as though it came from a separate study. For example, most of the studies report results separately for children of more than a specific age, so the results for each age group were included separately in the analysis. The potential limitations of including this type of data are discussed in section 12.6.

Continuous measures were centred on the mean (the mean value of each variable was subtracted from each of the individual measures), before including them in the regression model. Centering continuous variables in this way results in the constant (or intercept) of the regression model pertaining to the pooled estimate of the measure of effect when the explanatory variable takes its mean value.
A univariate analysis was undertaken in which each of the variables was included individually in the regression model with the measure of effect. The random effects meta-regression models (mixed models) were implemented to combine studies. Although age is related to tooth type (primary or permanent) both were included in the univariate analyses because the 8 year-old age group could have primary and/or permanent teeth. However, neither of the multivariate models included both terms.

A measure of the between study variance (heterogeneity) remaining after the variables included in the model had been accounted for was calculated using restrictive maximum likelihood estimation. Variables which showed a statistically significant association with the measure of effect (MD or RD) at the 15% statistical significance level (p<0.15) in the univariate analysis were included in the multivariate analysis. This significance level was chosen to conservatively identify variables that could potentially be important in the multivariate model. The multivariate analysis was carried out using a step-down analysis in which each variable was included in the initial model. Variables were dropped one by one, with the variable that showed the least evidence of a statistically significant association dropped first, until only variables which showed a statistically significant association at the 5% level were included in the analysis. The analysis was repeated using a step-up analysis to confirm the results of the step-down analysis. As a further exploratory analysis study validity was forced into the regression model as the effect of study validity was considered to be very important in these studies of variable quality. However, study validity was not found to be statistically significantly associated with the dependent variable in the analysis of dmft/DMFT score. The results of this analysis are presented in Appendix L.

4.6.1 Proportion (%) of caries-free children

A total of 31 RD estimates from 9 studies were included in the analysis. Several of these RD estimates came from the same study as each study provided estimates for more than one age group.

4.6.1.1 Univariate analysis

The results of the univariate analysis are shown in Table 4.6.

Table 4.6 Results of the univariate meta-regression analysis for the proportion of caries-free children

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category or mean</th>
<th>Constant (95%CI)</th>
<th>p-value of constant</th>
<th>Co-efficient (95%CI)</th>
<th>p-value of co-efficient</th>
<th>Between study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variables (pooled estimate)</td>
<td></td>
<td>15.4 (10.8, 20.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>163.0</td>
</tr>
<tr>
<td>Baseline %caries-free subject *</td>
<td>19.4</td>
<td>15.5 (11.7, 19.3)</td>
<td>&lt;0.001</td>
<td>0.4 (0.2, 0.6)</td>
<td>&lt;0.001</td>
<td>105</td>
</tr>
<tr>
<td>Tooth type (n=29) *</td>
<td>Not stated</td>
<td>8.4 (0.4, 16.5)</td>
<td>0.039</td>
<td>13.4 (6.1, 23.6)</td>
<td>0.011</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Permanent</td>
<td></td>
<td></td>
<td>3.6 (-7.9, 15.2)</td>
<td>0.538</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting*</td>
<td>Taiwan</td>
<td>20.5 (9.6, 31.3)</td>
<td>&lt;0.001</td>
<td>-5.19 (-17.5, 7.1)</td>
<td>0.407</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td></td>
<td></td>
<td>1.17 (-15.2, 17.6)</td>
<td>0.889</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N. America</td>
<td></td>
<td></td>
<td>-20.3 (-37.9, -2.6)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study duration*</td>
<td>9.0</td>
<td>15.4 (10.9, 19.8)</td>
<td>&lt;0.001</td>
<td>1.30 (0.0, 2.6)</td>
<td>0.049</td>
<td>147</td>
</tr>
<tr>
<td>Year of final survey</td>
<td>1969</td>
<td>15.4 (10.8, 20.1)</td>
<td>&lt;0.001</td>
<td>0.24 (-0.2, 0.7)</td>
<td>0.279</td>
<td>162</td>
</tr>
<tr>
<td>Number of years since change in fluoridation status</td>
<td>0.5</td>
<td>13.3 (5.9, 20.7)</td>
<td>&lt;0.001</td>
<td>-2.1 (-7.6, 3.5)</td>
<td>0.462</td>
<td>165</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.8</td>
<td>15.5 (10.7, 20.2)</td>
<td>&lt;0.001</td>
<td>-0.23 (-1.6, 1.1)</td>
<td>0.739</td>
<td>167</td>
</tr>
<tr>
<td>Validity score*</td>
<td>5.2</td>
<td>15.5 (10.7, 20.2)</td>
<td>&lt;0.001</td>
<td>-1.17 (-10.0, 7.7)</td>
<td>0.796</td>
<td>168</td>
</tr>
<tr>
<td>Average temperature (°C)</td>
<td>11.7</td>
<td>15.4 (10.7, 20.2)</td>
<td>&lt;0.001</td>
<td>0.11 (-0.7, 1.0)</td>
<td>0.795</td>
<td>168</td>
</tr>
</tbody>
</table>

*Included in multivariate analysis
The p-value shows whether the co-efficient is statistically significantly different from 0. If it is not statistically significantly different from 0 then this variable is not statistically significantly associated with the dependent variable (i.e. RD of proportion of caries-free children). The between study variance shows the estimate of the heterogeneity which is left between the estimates of the MD after that variable has been controlled for.

The model in which no variables (other than the risk difference) were included shows the pooled estimate of the risk difference of the change in the proportion of caries-free children to be 15.5% (95% CI: 10.8, 20.1). This is the same as the measure that would be produced by a standard meta-analysis. However, the measure of between study variance (heterogeneity) is large and highly statistically significant (p<0.001) and so this value should be interpreted with extreme caution.

At the 15% statistical significance level the following variables showed a statistically significant association with the risk difference: tooth type, study duration, setting, and baseline proportion of caries-free children. The risk difference increased with increasing proportion of caries-free children at baseline and study duration, and was greater in permanent teeth than in primary teeth and than in studies in which tooth type was not stated. The risk difference also varied according to setting and was greater in Taiwan and the North America and lower in Europe and Chile. Age, number of years since change in fluoridation status, average temperature, study validity and year of final survey did not show an association with the risk difference of caries incidence. Study validity was forced into the regression model for the reasons discussed above.

### 4.6.1.2 Multivariate Analysis

The multivariate model shows the effect of each variable controlled for the possible effects of the other variables included in the model. The results of the multivariate analysis are shown in Table 4.7. All the variables were centered in the same way as in the univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category (mean)</th>
<th>Co-efficient (SE)</th>
<th>p-value</th>
<th>Between study Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td></td>
<td>14.3 (6.7, 21.9)</td>
<td>&lt;0.001</td>
<td>53.1</td>
</tr>
<tr>
<td>Baseline %caries-free children</td>
<td>19.4</td>
<td>0.61 (0.43, 0.80)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>-1.85 (-10.9, 7.2)</td>
<td>0.688</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. America</td>
<td>22.90 (10.7, 35.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td>-4.71 (-17.1, 7.7)</td>
<td>0.456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validity score</td>
<td>5.2</td>
<td>16.78 (8.9, 24.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

The proportion of caries-free children at baseline, setting and validity score show a statistically significant association at the 5% level with the risk difference of the proportion of caries-free children between fluoridated and control areas. These variables appear to account for a lot of the variation seen in the initial model where the measure of heterogeneity was 163. Including these variables in the regression model reduced the between study variance to 53. In this model the MD increases with increasing caries-free children at baseline, validity score and study duration, and is greatest in North America and Taiwan and is lowest in Europe and Chile. The model obtained using a step-up regression analysis was similar. The association of validity score with the risk difference is in the opposite direction in the univariate to that in the model presented above (negative association in the univariate, positive association in the multivariate). The reason for this is unclear but it is possible that this is related to the fact that setting, validity score and study duration will be the same for each analysis from the same study and thus some degree of colinearity is likely to exist between these three variables. It should also be noted that the association was not significant in the univariate analysis suggesting that one or more of the other variables included in the multivariate analysis act to confound the relationship between study validity score and the risk difference.

### 4.6.2 dmft/DMFT

#### 4.6.2.1 Univariate Analysis

A total of 16 MD estimates from 4 studies were included in the analysis. The results of the univariate analysis are shown in Table 4.8.
Table 4.8 Results of the univariate meta-regression analysis for dmft/DMFT score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category or mean</th>
<th>Constant (95% CI)</th>
<th>p-value of constant</th>
<th>Co-efficient (95% CI)</th>
<th>p-value of co-efficient</th>
<th>Between study Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variables (pooled estimate)</td>
<td></td>
<td>2.3 (1.8, 2.8)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>1.068</td>
</tr>
<tr>
<td>Baseline dmft/DMFT *</td>
<td></td>
<td>3.6</td>
<td>2.3 (1.9, 2.7)</td>
<td>&lt;0.001</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Setting*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.777</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td>1.3 (0.4, 2.2)</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9 (-0.3, 2.1)</td>
<td>0.135</td>
</tr>
<tr>
<td>N America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9 (0.4, 3.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5 (0.3, 2.8)</td>
<td>0.013</td>
</tr>
<tr>
<td>Study duration (years)*</td>
<td></td>
<td>10.7</td>
<td>2.3 (1.9, 2.8)</td>
<td>&lt;0.001</td>
<td>0.2 (0.03, 0.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Validity score*</td>
<td></td>
<td>5.3</td>
<td>2.3 (1.8, 2.8)</td>
<td>&lt;0.001</td>
<td>-1.0 (-1.9, 0.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>Age (years)*</td>
<td></td>
<td>9.5</td>
<td>2.3 (1.8, 2.8)</td>
<td>&lt;0.001</td>
<td>0.1 (-0.01, 0.3)</td>
<td>0.062</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td>13.3</td>
<td>2.3 (1.8, 2.8)</td>
<td>&lt;0.001</td>
<td>-0.1 (-0.6, 0.4)</td>
<td>0.707</td>
</tr>
<tr>
<td>Number of years since change in fluoridation status</td>
<td>-0.6</td>
<td>2.2 (1.3, 3.0)</td>
<td>&lt;0.001</td>
<td>-0.1 (-0.6, 0.4)</td>
<td>0.707</td>
<td></td>
</tr>
<tr>
<td>Year of final survey</td>
<td></td>
<td>1975</td>
<td>2.3 (1.8, 2.9)</td>
<td>&lt;0.001</td>
<td>0.0 (-0.1, 0.1)</td>
<td>0.906</td>
</tr>
<tr>
<td>Tooth type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.14</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td>2.3 (1.5, 3.2)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0 (-1.1, 1.1)</td>
<td>0.938</td>
</tr>
</tbody>
</table>

*Included in multivariate analysis

The model in which no variables (other than the MD) were included shows the pooled estimate of the MD in dmft/DMFT between the fluoridated and control areas to be 2.3 (95% CI: 1.8, 2.8). This is the same as the measure that would be produced by a standard meta-analysis. However, the measure of between study variance (heterogeneity) is large and highly statistically significant (p<0.001) and so this value should be interpreted with extreme caution.

At the 15% statistical significance level the following variables showed a statistically significant association with the MD: baseline dmft/DMFT, setting, study duration, validity score and age. The MD was highest in Taiwan and North America, followed by Germany and the UK. Study duration, age, and baseline dmft/DMFT score showed a positive association with the MD – as the value of these variables increased so did the MD. Validity score showed a negative association with MD with the lowest validity studies showing a greater MD.

4.6.2.2 MULTIVARIATE ANALYSIS

Table 4.9 Results of the multivariate meta-regression analysis for dmft/DMFT score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Co-efficient</th>
<th>p-value</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>2.61 (2.31, 2.91)</td>
<td></td>
<td>&lt;0.001</td>
<td>0.111</td>
</tr>
<tr>
<td>Baseline dmft/DMFT</td>
<td>3.6</td>
<td>0.37 (0.26, 0.48)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.5</td>
<td>0.11 (0.04, 0.18)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Study duration (years)</td>
<td>10.7</td>
<td>0.26 (0.18, 0.34)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Setting*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>-0.74 (-1.20, -0.29)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. America</td>
<td>-0.57 (-1.27, 0.13)</td>
<td>0.112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age, baseline dmft/DMFT, setting and study duration show a statistically significant association at the 5% level with the MD in the dmft/DMFT. These variables appear to account for a lot of the variation seen in the initial model where the measure of heterogeneity was 1.07. Including these variables in the regression model reduced the between study variance to 0.111. All of the variables except study setting showed a positive association with the MD – as each variable increases so does the MD. Setting shows that the MD was smaller in Germany and North America than in the UK. There was insufficient data for the effects of Taiwan to be investigated and this was dropped from the analysis. The analysis was repeated using a step-up analysis and produced similar results. Validity score was did not show a significant association with the MD in the multivariate model. The model in which study validity was included is presented in Appendix L. Forcing study validity into the model had very little effect on the co-efficients and standard errors of the other variables.
4.7 Numbers needed to treat

The number needed to treat (NNT) represents the number of children that need to receive the intervention for one person to benefit from the intervention. The NNT can be calculated by taking the inverse of the risk difference. This is the measure that was calculated for the meta-analysis of the proportion of caries free children above. In this case it represents the number of people exposed to fluoridation for one additional child to be caries-free. An NNT is valid only for the comparison it is based on, for example water fluoride levels < 0.7 ppm versus 0.7 to 1.2 ppm.

The risk difference was calculated for each study comparison – for some studies more than one risk difference was calculated if caries measurement was made in more than one age group. A meta-analysis was conducted to provide a pooled estimate of the mean risk difference between the exposed and control groups. This was carried out for all teeth types combined (permanent, primary and not stated) and separately for permanent and primary teeth. Heterogeneity was investigated and found to be statistically significant in all models (the Q statistic) and so the results of these analyses should be interpreted with caution.

Table 4.10 Meta analysis of risk difference in the proportion (%) of caries-free children

<table>
<thead>
<tr>
<th>Tooth type</th>
<th>Age</th>
<th>Number of studies</th>
<th>Risk Difference % (95% CI)</th>
<th>Q-statistic – measure of heterogeneity</th>
<th>P-value for heterogeneity at the 5% level</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>31</td>
<td>15.5 (10.7, 20.2)</td>
<td>1421.0</td>
<td>&lt;0.001</td>
<td>6 (5, 9)</td>
</tr>
<tr>
<td>Primary</td>
<td>All</td>
<td>15</td>
<td>11.4 (6.5, 16.3)</td>
<td>354.4</td>
<td>&lt;0.001</td>
<td>9 (6, 15)</td>
</tr>
<tr>
<td>Permanent</td>
<td>All</td>
<td>16</td>
<td>19.1 (11.4, 26.7)</td>
<td>751.3</td>
<td>&lt;0.001</td>
<td>5 (4, 9)</td>
</tr>
<tr>
<td>Primary</td>
<td>5</td>
<td>11</td>
<td>13.2 (6.8, 20.0)</td>
<td>137.5</td>
<td>&lt;0.001</td>
<td>8 (5, 15)</td>
</tr>
<tr>
<td>Primary</td>
<td>8</td>
<td>4</td>
<td>7.2 (-3.6, 18.0)</td>
<td>211.3</td>
<td>&lt;0.001</td>
<td>14 (6, ∞)</td>
</tr>
<tr>
<td>Permanente</td>
<td>8</td>
<td>4</td>
<td>35.6 (22.4, 48.8)</td>
<td>39.1</td>
<td>&lt;0.001</td>
<td>3 (2, 5)</td>
</tr>
<tr>
<td>Permanente</td>
<td>6</td>
<td>12</td>
<td>13.1 (0.8, 25.5)</td>
<td>215</td>
<td>&lt;0.001</td>
<td>8 (4, 125)</td>
</tr>
<tr>
<td>Permanente</td>
<td>14-15</td>
<td>4</td>
<td>8.8 (0.7, 16.9)</td>
<td>36.8</td>
<td>&lt;0.001</td>
<td>11 (6, 143)</td>
</tr>
</tbody>
</table>

The numbers needed to treat with 95% confidence intervals are given in the final column of Table 4.10. For all teeth combined 6 people need to receive fluoridated water for one extra person to be caries-free, with a 95% confidence interval of between 5 and 9 people. Due to the heterogeneity the median risk difference was calculated for all teeth combined, for primary teeth and for permanent teeth. This was translated into a number needed to treat. The median NNT for all teeth combined was 6, for primary teeth was also 6 and for permanent teeth was 5. These numbers are very similar to those obtained using the meta-analysis suggesting that these figures are a relatively accurate estimation based on the data from the studies included in this analysis.

To investigate whether including estimates for multiple ages from one study in the meta-regression as if they were independent was leading to bias in the result, NNTs were calculated separately for each tooth type and age group (Table 4.10). The NNT was greater in primary than in permanent teeth and within permanent teeth increased with age. This would be expected as the univariate meta-regression showed that age had a negative association with the risk difference (and hence a positive association with the NNT), although this relationship was not significant in the multivariate analysis. The estimates of the risk difference were positive for all age groups reported. The variation in RD and NNT suggests that although there may have been some bias introduced by including estimates for multiple ages from the same study as if they were independent, this does not alter the conclusion that the overall effect is positive.

4.8 Publication bias

Although it is possible to create a funnel plot from the studies including the proportion (%) of caries-free children this has not been done because some studies would contribute several points, this would make the funnel plot difficult to interpret. It would be possible to take only one point from each study but this would only give nine points that would also lead to problems with regard to interpreting the plot. It is thus difficult to estimate whether publication bias is having an effect. It has been argued that it is easier to get a study published that shows a beneficial effect of water fluoridation. However, considering the broad approach to searching for studies and the inclusion of unpublished studies in this report it is unlikely that any major studies on the association of dental caries with water fluoridation have been missed. Importantly, any missed study would have to be very large, and very different to those that were included to overturn the overall result.
4.9 Discussion

Objective 1 attempts to assess the effect of water fluoridation on the development of caries. A small number of studies meeting the pre-defined criteria were found. While many cross-sectional studies exist, relatively few studies were designed to assess the effects of water fluoridation over time. Studying populations exposed or not exposed to water fluoridation longitudinally allows baseline dental health to be taken into account and differences developing over time to be assessed. Studies that assess dental caries at one point in time using an ecological or cross-sectional study design only show the differences in caries prevalence at that particular point in time. In such studies it is not possible to tell whether the observed differences have always existed between these populations or whether they are the result of the differing levels of water fluoride content between the study areas.

When diagnosing caries it is usual to have very specific written criteria. However, these criteria vary from study to study. In particular, they have changed over time as treatment philosophies have also changed. This means that there is likely to be inter-study variation in the threshold at which caries is diagnosed. What is more important is whether the diagnostic criteria have remained the same within studies. As this systematic review has used the difference in change between DMFT/dmft the intra-study variation is likely to be of minimal importance.

For this objective, the quality of studies found was only moderate (level B). A large number of studies were excluded because they were cross-sectional studies and therefore did not meet the inclusion criteria of being evidence level B or above. All but one of the studies included were before-after studies; three included studies used a cohort design, two prospective and one retrospective. The most serious defect of these studies was the lack of appropriate analysis. Many studies did not present an analysis at all, while others only did simple analyses without attempting to control for potentially confounding factors. Although the size of the differences found might be affected by confounding factors, the differences estimated in this review were sufficiently large that it is unlikely that confounding factors would account for them entirely. While some of these studies were conducted in the 1940’s and 50’s, prior to the common use of such analyses, studies conducted much later also failed to use methods that were commonplace at the time of the study. As an example, no study used an analysis that would control for the frequency of sugar consumption or the number of erupted teeth per child. Another defect of many studies was the lack of any measure of variance for the estimates of decay presented. This was not so much of a problem for the studies, which presented the proportion of caries-free children, as all these studies contained sufficient data to calculate standard errors for the data provided. However, for the studies that presented dmft/DMFT scores this was more of a problem with only four of the eight studies providing any estimate of variance.

To have clear confidence in the ability to answer the question in this objective, the quality of the evidence would need to be higher. The failure of these studies to deal with potential confounding factors or to provide standard error data means that the ability to answer the objective is limited.

Tables 4.1 to 4.3 and Figures 4.1 and 4.2 suggest, through a simple qualitative method of analysis, using means, and confidence intervals where available, that water fluoridation does appear to reduce caries. Table 4.4 shows that when water fluoridation is stopped, in 12 out of 16 studies the direction of the association is that the caries burden increases more in the previously-fluoridated groups than in the never fluoridated groups. Only eight of these studies provided a measure of the significance of this association and of these, four showed a statistically significant positive effect. When fluoridation is discontinued caries prevalence appears to increase in the area that had been fluoridated compared with the control area. Interpreting from this data the degree to which water fluoridation works to reduce caries is more difficult.

The meta-analysis showed a statistically significant effect of water fluoridation in reducing dental caries as measured by both dmft/DMFT and the proportion of caries-free children. However, the results showed statistically significant evidence of heterogeneity and thus the pooled estimates should be interpreted with caution. The meta-regression carried out to investigate the heterogeneity between studies showed that, for both dmft/DMFT and the proportion of caries-free children, the baseline caries measurement and study duration both accounted for a significant proportion of this heterogeneity. For both these outcome measurements, increased duration of follow up was associated with a greater difference in the change in caries measurement from baseline to final examination in the fluoridated compared with the control group.
The baseline measure of dental caries also showed a positive association with the mean difference. This is what would be expected for dmft/DMFT: the greater the population prevalence of tooth decay at the baseline examination the greater the effect of water fluoridation in decreasing this decay in the fluoridated area. However, the situation is slightly more complex for the proportion of caries-free children. The results suggest that the greater the proportion of caries-free children at baseline (i.e. the less decay in the population) the greater the change in the mean difference. This is possibly related to the distribution of caries-free children within a population. A population with a high proportion of caries-free children will also probably have more children with few decayed teeth than a population with a small proportion of caries-free children, which is likely to have more children with more decayed teeth. Such a population would only require a small decrease in decay for a noticeable increase in the proportion of caries-free children.

The meta-regression of the proportion of caries-free children found that setting accounts for a significant proportion of the heterogeneity. The results showed that the mean difference was highest in North America. However, this variable was the same for each analysis from the same study and so some caution should be exercised in interpreting these results. Average temperature and age were also statistically significantly associated with the mean difference in the meta-regression of the mean difference in dmft/DMFT. Both of these variables showed a positive association with the mean difference. Temperature was the same for each analysis from the same study; this may be a particular problem for these data as the 16 measures included in the analysis came from only four studies, and so the results for this variable should also be interpreted with caution.
If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Studies carried out after 1974 were selected to examine the effect of water fluoridation over and above the effect of other sources of fluoride, especially fluoridated toothpaste. As toothpaste containing fluoride was being widely used in industrialised countries by the early 1970’s, examining the effect of water fluoridation after 1974 should allow for any modifying effect of fluoride toothpaste and other sources of dental fluoride (e.g. mouthrinses, tablets) to be apparent. Studies carried out post-1974 which were conducted in industrialised countries were considered to have included the effects of these sources of fluoride, unless the study stated otherwise. Of the 24 studies that met the inclusion criteria for Objective 1, ten were completed after 1974 (1978 – 1997). The mean validity score of these ten studies is 5.0 (range 3.5 to 6.8 out of 8). Five of these studies were conducted in the UK (Wragg 1992; Attwood 1988; Hardwick 1982, Hobbs 1994; Gray 1999). The others were from the Netherlands, Finland, Germany, and Taiwan. Among these were eight before and after studies and two cohort study (Hardwick 1982, Maupomé 2000). Six of the before and after studies examined the discontinuation of water fluoridation.

The results of the studies in which fluoridation was initiated and which were completed after 1974 are displayed in Table 5.1. The results of the studies in which fluoridation was discontinued during this time period are presented in Table 5.2. In addition to the ten studies outlined above, two studies (Gray, 2000 and Holdcroft, 1999) met inclusion criteria but direct comparison data could not be extracted and were excluded from this table. The results of these studies can be found in Table 4.5 in chapter 4.

Table 5.1 Caries studies of fluoridation initiation, completed after 1974

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Teeth Type</th>
<th>Mean Difference (95% CI)</th>
<th>Year of final survey</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo (1984)</td>
<td>5</td>
<td>Primary</td>
<td>-2.0 (-6.4, 2.4)</td>
<td>1971 - 1984</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>64.1 (55.4, 72.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Primary</td>
<td>0.4 (-4.8, 5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Primary</td>
<td>28.5 (20.5, 36.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>34.4 (19.7, 49.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>5</td>
<td>Primary</td>
<td>26.0 (19.4, 32.6)</td>
<td>1988 - 1997</td>
<td>3.5</td>
</tr>
<tr>
<td>dmft/DMFT Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo (1984)</td>
<td>5</td>
<td>Primary</td>
<td>3.6 (2.6, 4.6)</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>1.6 (1.4, 1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Primary</td>
<td>4.4 (3.9, 4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>2.6 (2.2, 3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>3.8 (2.7, 4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort Study: Difference in Increment in DMFS/DMFT score (Control – Fluoridated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardwick (1982)</td>
<td>12</td>
<td>Permanent</td>
<td>DMFS 2.5 (1.0, 3.9)</td>
<td>1974 - 1978</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>DMFT 1.1 (0.4, 1.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of the six studies assessing the proportion of caries-free children, five studies found the direction of association of water fluoridation and caries to be positive. Four of these found a statistically significant benefit. One study found the direction of association to be negative, but this effect was not statistically significant. All of the five analyses investigating the mean difference in dmft/DMFT were from the same study (Guo, 1984). All found a statistically significant positive association between water fluoridation and the mean difference in the change in dmft/DMFT. The cohort study of water fluoridation initiation found a statistically significant difference in the increment in both DMFT and
DMFS scores between the fluoridated and control area with the control area showing the greatest increment (Hardwick, 1982).

Table 5.2 Caries studies in which fluoridation was discontinued completed after 1974

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Teeth Type</th>
<th>Mean Difference (95% CI)</th>
<th>Year of final survey</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>proportion of caries-free children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunzel (1997)</td>
<td>8</td>
<td>Permanent</td>
<td>8.6 (-5.3, -2.5)</td>
<td>1991 - 1995</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>dmft/DMFT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attwood (1988)</td>
<td>10</td>
<td>Permanent</td>
<td>-0.6 (-1.3, 0.1)</td>
<td>1980 – 1986</td>
<td>4.8</td>
</tr>
<tr>
<td>Hobbs (1994)</td>
<td>5</td>
<td>Primary</td>
<td>-1.2</td>
<td>1989 - 1993</td>
<td>4.5</td>
</tr>
<tr>
<td>Kunzel (1997)</td>
<td>12</td>
<td>Permanent</td>
<td>0.1</td>
<td>1991 - 1995</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>-0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Permanent</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wragg (1992)</td>
<td>5</td>
<td>Primary</td>
<td>-1.5 (-2.2, -0.7)</td>
<td>1985 – 1995</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>DMFS score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seppa (1998)</td>
<td>6</td>
<td>Not stated</td>
<td>-0.1</td>
<td>1992 - 1995</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Permanent</td>
<td>0.2 (-0.5, 0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Permanent</td>
<td>-1.1 (-2.3, 0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Permanent</td>
<td>-0.9 (-4.2, 2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Mean Difference in D1D2MFS</em> Scores</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maupomé (2000)</td>
<td>8</td>
<td>Permanent</td>
<td>0.59 (0.41, 0.77)</td>
<td>1993 – 1997</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td>1.39 (0.23, 2.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>D1D2MFS</em> Incidence</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maupomé (2000)</td>
<td>11</td>
<td>Permanent</td>
<td>0.13 (-0.07, 0.34)</td>
<td>1993 – 1997</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td></td>
<td>0.47 (-0.02, 0.96)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*D1D2MFS is a modified DMFS score where D1 = an incipient lesion, D2 = a cavitated lesion

There were 20 analyses looking at the discontinuation of water fluoridation, four of which looked at the proportion of caries-free children, seven looked at the dmft/DMFT score, five looked at the DMFS score and four reported on the D1D2MFS score. Of these 20 analyses, 12 found the direction of association to be positive (ie a greater increase in caries in the area that had been fluoridated compared with the control area). Twelve of the 20 analyses provided a measure of the significance of the association, four of the studies found a statistically significant positive association. Four analyses from a single study (Maupomé 2000) found the direction of association to be negative (the level of caries improved more in the area that discontinued fluoridation than in the area that was never fluoridated). Two of these results (from the before-after study but not in the cohort study) were statistically significant.

In the development of both of the meta-regression models of caries for Objective 1, the baseline disease level was included and found to be statistically significant. At lower levels of disease the reduction of dmft/DMFT was less in fluoridated areas than in non-fluoridated areas but there was a larger increase in the number of children found to be caries-free. Both of these differences were statistically significant. If other sources of fluoride are shown to have an effect on dental caries then decay should drop, thus baseline levels of decay would be at lower levels than when many of the original studies looking at water fluoridation were started. Water fluoridation would thus be expected to have less of an effect on the severity of dental caries, as measured by the dmft/DMFT score, but would be expected to have a greater effect on the proportion of caries-free children (see discussion section of chapter 4). Year of final study was also included as an explanatory variable in the univariate meta-regression for both the caries-free and dmft/DMFT analysis. This variable did not show any evidence of a significant association with the mean difference and so was not included in the multivariate analysis.
5.1 Discussion

This objective assesses the impact of water fluoridation on caries after the advent of other sources of fluoride, especially toothpaste containing fluoride. Relatively few studies qualified to address this issue (10). None of these identified this objective as the purpose of the study, but were conducted in time periods and countries where fluoridated toothpaste use was widespread. No included study specifically measured fluoride exposure from sources other than water although Hardwick (1982) reported the use of fluoridated toothpaste in both groups. The studies included for Objective 2 are a subset of those in Objective 1. The studies included in Objective 2 are of moderate quality (level B). Aside from design issues, their major failing was lack of analyses controlling for exposure to other sources of fluoride, including toothpaste.

While only ten studies were included for Objective 2, these would be enough to provide a confident answer to the objective’s question if the studies were of sufficient quality. Since these studies were completed after 1974, one might expect that the validity assessments would be higher than the earlier studies due to the introduction of more rigorous study methodology and analytic techniques. However, the average validity checklist score and level of evidence was essentially the same for studies completed after 1974 as the whole group of caries studies. Hence, the ability to answer this objective is similar to that in Objective 1.

In examining the post-1974 studies (Table 5.1), the evidence suggests that water fluoridation has an effect over and above that of fluoridated toothpaste (and other sources of fluoride). If fluoridated toothpaste was responsible for reducing the difference in baseline caries between fluoridated and non-fluoridated areas, then the meta-regression models created for Objective 1 suggest that at lower levels of caries the reduction in DMFT would be less but the proportion of caries-free children would be greater. The study included in the review with the highest validity score (Hardwick 1982) showed a statistically significant difference in caries increment between fluoridated and non-fluoridated areas. Those in the non-fluoridated area had the greatest increment, in spite of fluoridated toothpaste being used by both groups (94% vs 95% used only fluoride toothpaste in the fluoridated and non-fluoridated groups, respectively).
Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations bringing equity

No level A studies, and very few level B studies for Objective 3 were identified by the search. Because the issue of social class effects of water fluoridation was considered highly important, studies of any level that were conducted in the UK were included. A total of 15 studies investigating the association of water fluoridation, dental caries and social class were identified, ranging in publication dates from 1969-1999. Among these were three unpublished studies (Holdcroft 1999; Gray 2000, Jones 2000). Details of baseline information and results from each study can be found in tables in Appendix C. All but three of the included studies were cross-sectional in design. These three were before-after study designs (DHSS, 1969; Holdcroft, 1999; Gray, 2000). Seven of the studies presented measures of caries experience (proportion (%) of caries-free children, DMFT and dmft) stratified according to the Registrar General's social class classification (see Appendix H). Of these studies, five examined caries experience in children aged five, and two also examined 8, 12 and 14 year-olds. One study studied 10 year-olds only and another 15-16 year-olds only. Two studies presented data in a similar way but used different methods of classifying social class (low versus high deprivation and urban ordinary versus social priority). Urban ordinary and social priority was a classification used by the education authority to classify its schools at the time of the study, with social priority indicating less privileged students. Two studies used a regression analysis to investigate the association of caries experience (dmft and DMFT) with a measure of social deprivation (Jarman and Townsend scores, section 6.3), separately for high and low fluoride areas. The remaining two studies presented dmft and proportion caries-free data for a sample of fluoridated and non-fluoridated areas together with the Jarman score for each area, before and after water fluoridation was introduced in some of these areas.

If water fluoridation results in a reduction in caries across social class, reducing social inequalities in dental health, these studies would be expected to show that caries experience is lower in fluoridated than non-fluoridated areas. Importantly, the difference in caries experience between the social classes would be less in the fluoridated than in the non-fluoridated areas.

All except two of the studies investigating the association between caries experience, water fluoridation and social class were of evidence level C. The only exceptions were the before-after studies, which were level B. The average checklist score was 1.6 out of 8 (range 0.8 to 5.3), with eight of the 12 studies scoring only 0.8. Only two of the studies were prospective, had a baseline survey and follow-up and so the remaining studies lost marks for these checklist items. Only one study reported reliable measurement (or adequate reporting) of the fluoride concentration. None of the studies attempted to control for confounding using multivariate analysis – the only confounders considered were age (most studies presented results for one age only or stratified on age) and ethnic group (two of the studies only included children from one ethnic group).

Because there were very limited data available in formats that allowed pooling of results using meta-analytic techniques a more simple approach was adopted. For studies in which caries experience was presented by social class, as measured by the Registrar General’s grouping, some pooling was possible and the results of this are presented below. For the other studies a qualitative analysis has been presented.

6.1 Proportion (%) of caries-free children stratified by the Registrar General’s classification of social class

The proportion of caries-free children for each age group was determined by calculating the total number of children with no caries experience (caries-free), summing this number across studies and dividing by the sum of the total number of children from all studies. This method also allowed the calculation of a standard error and confidence interval. The results of this analysis are presented in Table 6.1. The studies included were Bradnock, 1984; Carmichael, 1980; DHSS, 1969; Evans, 1996;
Murray, 1984; and Murray, 1991. If there were several studies from one geographical area the most recent study for that age group was included. This decision was made in order to minimise the effect of any confounding variables operating in this area.

**Table 6.1** Proportion of caries-free children by social class and water fluoride level

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>Studies Included</th>
<th>Age</th>
<th>Social Class I &amp; II</th>
<th>Social Class III</th>
<th>Social Class IV &amp; V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Caries-free (95% CI)</td>
<td>Number</td>
<td>% Caries-free (95% CI)</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>5</td>
<td>55 (48, 63)</td>
<td>153</td>
<td>43 (37, 49)</td>
</tr>
<tr>
<td>High</td>
<td>Murray 1984</td>
<td>10</td>
<td>43 (31, 55)</td>
<td>67</td>
<td>29 (23, 35)</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>10</td>
<td>26 (16, 36)</td>
<td>80</td>
<td>26 (20, 32)</td>
</tr>
<tr>
<td>High</td>
<td>Murray 1991</td>
<td>15-16</td>
<td>31 (22, 40)</td>
<td>94</td>
<td>27 (20, 35)</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>15-16</td>
<td>23 (14, 32)</td>
<td>80</td>
<td>20 (13, 27)</td>
</tr>
</tbody>
</table>

With the exception of one study of 15 to 16 year-old children (Murray 1991, social classes IV & V), these results show that for all age groups and all social classes the proportion of caries-free children is higher in the fluoridated than in the non-fluoridated areas. With the exception of the same study, caries experience is higher in the lower social classes (social class IV and V) than the higher social classes in both fluoridated and non-fluoridated areas. In most of the age groups, and for both high and low fluoride areas, a gradient relationship exists between social class and the proportion of caries-free children, this is illustrated graphically for children aged five in Figure 6.1. Data from children aged five years were graphed as four studies were included which looked at the association of water fluoride level, social class and caries experience in children of this age. Only two studies were found for other age groups, one each for ages 10 and 15-16.

**Figure 6.1** Proportion of (%) caries-free five-year-old children (95% CI) by social class in high and low fluoride areas

Figure 6.1 illustrates the higher proportion of caries-free children aged five years in the areas receiving fluoridated water compared with those receiving water with a low fluoride concentration. It also shows the increase in caries experience across the social classes for children aged 5 years. The absolute difference in the proportion (%) of caries-free children between Classes I & II and IV & V in the fluoridated group is 20%, while it is 18% in the non-fluoridated group. Thus there is no evidence from these studies to suggest that fluoridation reduces the social gradient.
6.2 dmft/DMFT stratified by the Registrar General’s classification of social class

The mean number of dmft/DMFT per child for each age-group was determined by calculating the total dmft/DMFT in each study, summing this number across studies and dividing by the sum of the total number of children from all studies. This method did not allow the calculation of a standard error, and too many of the studies did not provide information on standard errors to allow this to be estimated. For children aged five, results from seven study analyses contributed to this analysis (from Bradnock 1984; Carmichael 1980; Carmichael 1989; DHSS 1969; and Evans 1996). For 8, 12 and 14 year-olds, two analyses contributed (DHSS 1969, England and Wales data). However, for ages 10 and 15-16 data were only available from one study each (Murray 1984; Murray 1991). The results of this analysis are presented in Table 6.2.

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>Studies Included</th>
<th>Age</th>
<th>Social Class I &amp; II</th>
<th>Social Class III</th>
<th>Social Class IV &amp; V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DMFT Number</td>
<td>DMFT Number</td>
<td>DMFT Number</td>
</tr>
<tr>
<td>High</td>
<td>Bradnock 1984;</td>
<td>5</td>
<td>1.1 343</td>
<td>1.9 388</td>
<td>1.8 227</td>
</tr>
<tr>
<td></td>
<td>Carmichael 1980;</td>
<td>5</td>
<td>1.8 292</td>
<td>3.1 383</td>
<td>3.8 241</td>
</tr>
<tr>
<td></td>
<td>Carmichael 1989;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>DHSS (England)</td>
<td>8</td>
<td>1.0 39</td>
<td>1.3 98</td>
<td>1.6 47</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.2 49</td>
<td>2.0 88</td>
<td>2.2 37</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Murray 1984</td>
<td>10</td>
<td>1.5 67</td>
<td>1.7 249</td>
<td>1.6 99</td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>1.8 80</td>
<td>2.0 225</td>
<td>2.0 163</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>DHSS (England)</td>
<td>12</td>
<td>3.6 15</td>
<td>3.5 47</td>
<td>3.5 17</td>
</tr>
<tr>
<td>Low</td>
<td>12</td>
<td>5.3 15</td>
<td>5.6 27</td>
<td>5.1 10</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>DHSS (England)</td>
<td>14</td>
<td>5.5 8</td>
<td>5.5 17</td>
<td>5.0 8</td>
</tr>
<tr>
<td>Low</td>
<td>14</td>
<td>6.8 13</td>
<td>7.8 29</td>
<td>6.5 8</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Murray 1991</td>
<td>15-16</td>
<td>2.2 94</td>
<td>2.7 135</td>
<td>3.3 35</td>
</tr>
<tr>
<td>Low</td>
<td>15-16</td>
<td>2.9 80</td>
<td>3.4 140</td>
<td>3.9 57</td>
<td></td>
</tr>
</tbody>
</table>

These results show that for all age groups and all social classes the dmft/DMFT is lower in the fluoridated than in the non-fluoridated areas. On average there is more caries in the lower social classes (social class IV and V) than the higher social classes. In most of the age groups, and for both high and low fluoride areas, a gradient relationship exists between social class and the dmft/DMFT score, this is illustrated graphically for children aged five in Figure 6.2. As above children aged five were selected for further analysis as seven analyses were included for children of this age while data were only available from one or two analyses for each of the other age groups.

![Figure 6.2](image-url)  
Figure 6.2  dmft by social class in high and low fluoride areas for children aged 5 years
Figure 6.2 illustrates the lower dmft in the areas receiving fluoridated water compared with those receiving water with a low fluoride concentration. It also shows the increase in caries experience across the social classes. The social class gradient is steeper in the low fluoride areas, in contrast to the proportion (%) of caries-free children graph. These data from 5-year-old children suggest that water fluoridation is leading to a decrease in dmft across the social classes and reducing the inequalities in dental health between the social classes. However this trend is not seen in the other age groups. It may be a finding peculiar to the younger age group or it may be because only a very small number of studies were included in the older age groups.

6.3 Other studies looking at dental decay, water fluoridation and social class

Two studies of five year-old children (Provart, 1995; and Rugg-Gunn, 1977) present results in a similar way to those outlined above but use different classifications of social class. The Provart study used the Townsend index (see Appendix H) to classify social deprivation, and then grouped the children into two groups, ‘low’ and ‘high’ deprivation. The cut-off used for this classification was not stated in the article. The Rugg-Gunn study used a classification system that was currently being used by the school system. Schools were classified as ‘ordinary’ or ‘social priority’. Full details of these classifications were not given. These studies both show decreased caries experience in the fluoridated compared with the non-fluoridated areas. Comparing the fluoridated areas, Provart (1995) shows greater caries experience (measured by both dmft and proportion of caries-free children) in areas of ‘high deprivation’ compared with areas of ‘low deprivation’. This finding is not confirmed by the Rugg-Gunn study, which did not find any difference in caries experience (dmft and proportion of caries-free children) in areas defined as ‘social priority’ compared with areas defined as ‘urban ordinary’.

A regression analysis approach was used in two studies, one of which was later re-analysed using a different measure of social deprivation (Riley, 1999; and Jones, 1997 and 2000). Riley selected five year-olds in seven fluoridated areas and seven non-fluoridated areas and calculated the slopes and intercept of the regression line, plotting mean dmft versus Townsend score for all fluoridated areas and all non-fluoridated areas. The slope of the regression line was positive in both groups of areas (the higher the deprivation scores the higher the dmft score) and the y intercept was lower in fluoridated areas (0.77 vs 1.7 for non-fluoridated areas). This means that the dmft experience is lower in fluoridated areas for all levels of deprivation. The slope of the regression line was statistically significantly less steep in the fluoridated areas than in the non-fluoridated areas (beta coefficient 0.08 vs 0.17, p < 0.001). This suggests that dental decay increases with increased social deprivation (as measured by the Townsend index), that dental decay is greater in non-fluoridated compared with fluoridated areas and that the difference in dental decay between the fluoridated and non-fluoridated areas increases with increased social deprivation.

The Jones 1997 study used data on five and 12 year-olds and calculated similar regression lines using the Jarman index. This study showed similar findings to the Riley study for dmft/DMFT scores. Dental decay had a significantly negative relationship with water fluoridation, and a significantly positive association with social deprivation. In this study, water fluoridation was also found to reduce the effect of deprivation. An unpublished report (Jones 2000) reassessed the impact of water fluoridation on caries by deprivation level using the same caries data for 12 year-old children, but classifying deprivation by the Townsend index rather than the Jarman index. The findings of the original study were confirmed, finding that the more deprived areas achieved greater reductions in tooth decay with water fluoridation than less deprived areas.

The Gray (2000) and Holdcroft (1999) reports present similar before-after data, comparing the dmft of children aged five before the introduction of water fluoridation in a selection of areas and 10 years after water fluoridation had been introduced. Jarman scores were presented for each area (based on the 1991 census). The authors have not presented enough suitable data for making comparisons. In particular, the areas that met inclusion criteria for having a baseline survey within one year of starting fluoridation were limited. In addition, none of the non-fluoridated areas presented had Jarman scores above zero, while the fluoridated areas had mixed Jarman scores. Matching fluoridated and non-fluoridated areas within these data sets is difficult due to the wide variation in Jarman scores, proportions of populations fluoridated, and starting dates of fluoridation.

The Beal 1971 study presents before and after data comparing the decayed, extracted and filled teeth (deft) and proportion of caries-free children aged five before the introduction of water fluoridation in
two of three areas and three years later after water fluoridation had been introduced. One of the fluoridated areas is described as poorer and with a higher proportion of immigrants. The other two areas (one fluoridated, one not) are described as industrial areas. While there is no formal assessment of social class, the findings of this study are presented for comparison. The mean change in deft score in the poorer fluoridated area was larger than in the fluoridated industrial area (difference of 3.22 compared with 2.46). The change in the percent caries-free was also larger in the poorer group (difference of 39% compared with 13%). This implies that the effect is greater in the lower social classes.

6.4 Discussion

The number of UK studies with adequate social class data (15) was very small. Many other studies mentioned social class in some way, such as the typical occupations of the ‘head of the house’, or simply stated that social class in the areas being compared was similar. The quality of the evidence of the studies was low (all but 4 were level C), and the measures of social class that were used varied. Most of the studies that had enough information on social class to be evaluated were cross-sectional, with two before-after studies. Additionally, some of the included studies did not record individual exposure to water fluoride but were based on an ecological analysis, which is likely to be less accurate. Variance data were not reported for dmft/DMFT scores in these studies, so a statistical analysis was not undertaken. While these studies provide an indication of the effect, the ability to answer this question is low.

The effect of water fluoridation in reducing the difference in dental health between social classes classified by the Registrar General’s classification shows varying effects. In the proportion of caries-free children analysis (Table 6.1 and Figure 6.1), a positive effect of water fluoridation is seen among children aged five years in all social classes. However, the difference between the classes does not vary between the high and low fluoride areas. In the mean change of dmft/DMFT analysis (Table 6.2 and Figure 6.2), water fluoridation does appear to be having an impact on reducing the differences between the social classes among children aged five years. In Figure 6.2 the slopes of the two lines are divergent, indicating a greater effect in the lower social classes (IV and V). This effect was not seen in 10 and 15-16 year-olds.

Two studies using regression analysis (presented in three analyses, Riley 1999; Jones 1997, Jones 2000) found similar effects on dmft/DMFT scores among five and 12 year-olds using measures of social deprivation (Townsend and Jarman indices) rather than the Registrar General’s classification. These studies reported a statistically significant greater effect in the most deprived groups.

The meta-regression analysis reported in chapter 4 is also relevant to the discussion of the effect of water fluoridation on inequities in levels of dental caries. One of the findings of the social class studies is that people of lower social class had higher levels of dental caries. Thus their caries baseline score is higher. The results of the meta-regression analysis suggests that these children would have a higher reduction in mean dmft/DMFT but a lower reduction in the number of children who are caries-free. The meta-regression is based upon studies of stronger design than the majority of studies included in these analyses.

The small quantity of studies, differences between these studies, and their low quality rating, suggest caution in interpreting these results. There appears to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in five and 12 year-olds, using the dmft/DMFT measure. This effect was not seen in the proportion of caries-free children among five year-olds. There were not sufficient data for the effects in children of other ages to be investigated fully.
Objective 4: Does water fluoridation have negative effects?

Any study of a potential negative effect of fluoridation that met inclusion criteria was reviewed. However, more studies were found and included on fluorosis, bone fracture, and cancer than other outcomes. This objective was broken down into four sections, fluorosis, bone fracture (and bone development effects), cancer and other possible adverse effects.

7. DENTAL FLUOROSIS

A total of 88 studies looking at the association of dental fluorosis with water fluoridation met inclusion criteria. Most of these studies examined children, but a few studied adults or did not state the age studied. Four of these studies used a before-after study design, one was a case-control study and the rest were cross-sectional studies in which the prevalence of dental fluorosis was measured at one point in time in areas with different water fluoride concentrations. Of these, 14 did not state whether the water was artificially or naturally fluoridated, 20 compared areas artificially fluoridated to a level of 0.6–1.2ppm with areas with low (<0.3ppm) or very high (4-7ppm) natural fluoride content. The remaining studies compared naturally fluoridated areas. These studies were conducted in 30 countries. For this analysis, study areas with natural fluoride levels above 5ppm were excluded. This is significantly above the level recommended for artificial fluoridation. The range of 0 to 5ppm is broad enough to be able to explore whether a dose-response relationship exists. Details of baseline information and results from each study can be found in the tables in Appendix C. Twelve studies met inclusion criteria but were not included in the main analysis for various reasons, the results of these studies and the reasons for their exclusion from the main analyses are presented in section 7.4.

One study achieved evidence level B, all of the remaining studies looking at dental fluorosis were of evidence level C. The validity scores ranged from 1.3 to 5.8 with a mean score of 2.8 out of a possible 8. Only one study included a baseline survey at the time of a change in the water fluoride level of one of the study areas (the level B study). Only four studies used a prospective study design and only 16 of the studies used any form of blinding.

Because the studies used different indices to assess fluorosis, the percentage prevalence of fluorosis was selected as the outcome of interest. Using this measure, all children with some degree of fluorosis were classified as ‘fluorosed’ as opposed to normal. Using the different indices, children with a TSIF, T&F or DDE score greater than zero and Dean’s classification of ‘questionable’ or higher were classified as fluorosed. For the modified DDE index the number of children in the first category (‘all’) was taken as the number of children with dental fluorosis (see Appendix I). The term ‘fluorosis’ is used throughout this report, however it should be understood that the indices used to measure fluorosis also measure enamel opacities not caused by fluoride. Hence, the levels of fluorosis described here include some amount of overestimation of the prevalence of true fluorosis. This may be particularly true of those studies using the modified DDE index.

As there may be some debate about the significance of a fluorosis score at the lowest level of each index being used to define a person as ‘fluorosed’, a second method of determining the percent ‘fluorosed’ was selected. This method describes the number of children having dental fluorosis that may cause ‘aesthetic concern’. The level at which fluorosis was judged to cause aesthetic concern was taken from a study by Hawley (1996). Children from Manchester aged 14 were shown pictures of fluorosis classified using the T & F index and asked to rate the appearance of each as either very poor, poor, acceptable, good or very good. The cut-off point for this analysis was taken as the level of fluorosis above which the children classified the photographs as “very poor” or “poor”. This corresponded to a T & F score of three or more (Hawley, 1996). This was translated as being equivalent to Dean’s score of “mild” or worse and a TSIF score of two or more. This additional analysis was restricted to these three indices, as the definition was not transferable to the other fluorosis indices.

A regression analysis was used to investigate the association of water fluoride level with the prevalence of dental fluorosis (the analysis was conducted separately for the two measures of fluorosis outlined above). A multilevel model was used to combine studies. Each area with a different fluoride concentration under observation within a study was included separately in the model. The log
(odds) of having fluorosis/aesthetic fluorosis was modelled as a function of fluoride level. If the exact or average level of fluoridation was known this was included in the model. When a range of fluoridation level or an upper limit was provided the mid-value was used (for example if fluoridation was given as <0.7ppm, 0.35ppm was entered in the model for that group of people). When only a lower limit was given, 0.5ppm was added to this limit if it was less than 2ppm, and 1.0 was added if the limit was greater than 2ppm (e.g. if the level of fluoridation was given as >2.5ppm, then the level was entered as 3.5ppm). A sensitivity analysis was used to assess the robustness of the model's fit to the choice of values allotted to groups for which only lower limits were known. This was done by applying the lower limits themselves, and the lower limits +1.5ppm for levels with lower limits less than 2ppm, and 2ppm to groups with lower limits greater than 2ppm. The sensitivity analysis did not change the results of the analysis, so only the results of the main analyses are presented below.

The univariate regression model consisted of two parts. In the first, the standard fixed effect model, the log-odds of fluorosis was fitted as the outcome and the water fluoride level was fitted as the exposure variable. In the second, a random effects model was included to allow for the fact that some of the study areas came from the same studies (e.g. two low fluoride areas and four high fluoride areas from one study). Separate intercepts and slopes were permitted for each study by fitting these terms as random effects. In a similar fashion to more standard meta-analysis models, weighting of individual groups of people in the model was inversely proportional to the variance of the outcome estimate for that group. A normal distribution was assumed for the log odds for each group. Models were fitted using the 'PROC MIXED' procedure in the SAS software package, version 6.12 (SAS Institute Inc., USA). The algebraic form of the model used is presented in Appendix J.

The relationship between the log odds of aesthetic fluorosis and fluoride level appeared to be linear. However, the relationship between the log odds of fluorosis and the log of fluoride level appeared linear, and hence a log transformation of fluoride level was used in the model for this outcome. Both fluoride level and log fluoride level were centred before modelling.

A multivariate analysis was used to investigate possible sources of heterogeneity. This was similar to the univariate model in that it included two components, random and fixed effects. The effects of several potential factors were explored by including them as covariates in the above model. The effect of indices of fluorosis (e.g. Dean's), average age, source of fluoridated water (artificial, natural or both), mean altitude level, average temperature, type of teeth assessed (permanent, both, primary, not stated), method of assessment (clinical, photograph, both, not stated), study location (Europe, North America, S. America, Africa, Asia, Caribbean, Scandinavia, Australia), water source (public water, well, both, not stated), year of study report and study validity score were investigated.

The results of the analyses considering the proportion of people with any form of fluorosis and the proportion of people with fluorosis of aesthetic concern are presented separately.

7.1 Proportion of the population with dental fluorosis

7.1.1 Univariate analysis

The results of the univariate regression model are presented in Table 7.1

This model shows that log of the odds of the prevalence of dental fluorosis shows a positive linear association with the log of water fluoride level. Thus as water fluoride concentration increases so does the prevalence of dental fluorosis in the population. The random effects section of the model shows the variation between the intercepts and slopes fitted to the individual studies. Using this model, estimates with confidence intervals can be constructed for the proportion of persons in a population with fluorosis for a given level of water fluoridation.
Table 7.1 Results of the univariate analysis of the regression of water fluoride level against the proportion of the population with dental fluorosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Coefficient</th>
<th>Variance</th>
<th>Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.01</td>
<td>-0.440</td>
<td>0.030</td>
<td>0.644 (0.455 to 0.912)</td>
</tr>
<tr>
<td>Log fluoride level (centred by adding .526051)</td>
<td>0.0001</td>
<td>0.7155</td>
<td>0.0061</td>
<td>2.045 (1.750 to 2.390)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between study (intercept)</td>
<td></td>
<td></td>
<td></td>
<td>2.024</td>
</tr>
<tr>
<td>Between study (fluoride level – slope)</td>
<td></td>
<td></td>
<td></td>
<td>0.362</td>
</tr>
<tr>
<td>Covariance of intercept and slope</td>
<td></td>
<td></td>
<td></td>
<td>-0.412</td>
</tr>
</tbody>
</table>

This association is illustrated graphically in Figure 7.1. The size of the circles on the graph indicates the weighting of the study. Larger circles represent the larger studies.

![Graph showing the proportion of the population with dental fluorosis by water fluoride level.](image)

Figure 7.1 Proportion of the population with dental fluorosis by water fluoride level together with the 95% upper and lower confidence limits for the proportion

Examples of this model are illustrated in Table 7.2.

Table 7.2 The estimated proportion (%) of the population with dental fluorosis at different water fluoride concentrations

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>Proportion (%) of the population affected by dental fluorosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>15 (10, 22)</td>
</tr>
<tr>
<td>0.2</td>
<td>23 (17, 30)</td>
</tr>
<tr>
<td>0.4</td>
<td>33 (26, 41)</td>
</tr>
<tr>
<td>0.7</td>
<td>42 (34, 51)</td>
</tr>
<tr>
<td>1</td>
<td>48 (40, 57)</td>
</tr>
<tr>
<td>1.2</td>
<td>52 (43, 60)</td>
</tr>
<tr>
<td>2</td>
<td>61 (51, 69)</td>
</tr>
<tr>
<td>4</td>
<td>72 (62, 80)</td>
</tr>
</tbody>
</table>
These results show a strong association between water fluoride level and the proportion of the population with dental fluorosis. The model may not fit data at the extreme ends (low or high levels of fluoride) very well, due to the small numbers of data points. While many areas in Britain may have water fluoride levels lower than this, 0.4ppm has been chosen as the comparator (low fluoride) in subsequent analyses to ensure that the results are as reliable as possible. The effect of changing the water fluoride level of a low fluoride area with 0.4ppm fluoride in the water supply to an area with 0.7, 1.0 and 1.2ppm in the water supply is shown in Table 7.3

Table 7.3  Estimated difference in the proportion of the population with dental fluorosis at various levels of water fluoride concentration

<table>
<thead>
<tr>
<th>Fluoride ppm</th>
<th>Difference in proportions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 v 0.7</td>
<td>9.3 (-1.9, 20.6)</td>
</tr>
<tr>
<td>0.4 v 1.0</td>
<td>15.7 (4.1, 27.2)</td>
</tr>
<tr>
<td>0.4 v 1.2</td>
<td>18.9 (7.2, 30.6)</td>
</tr>
</tbody>
</table>

These results show that there are relatively large differences in the prevalence of dental fluorosis at the level of water fluoridation 0.7-1.2ppm when compared with an area with a relatively low water fluoride content (0.4 ppm). The differences in the prevalence of dental fluorosis at 1.0 and 1.2 compared with 0.4ppm are statistically significant (the confidence limits do not include 0). The numbers needed to harm (cause fluorosis) provide an estimate of the number of people that need to receive water fluoridated at the new level (compared to 0.4 ppm) for 1 extra person to have dental fluorosis. Increasing the level of water fluoride concentration from 0.4 to a slightly higher figure of 1.0 (the level which water is usually artificially fluoridated to) would lead to one extra person with dental fluorosis for every 6 people receiving the new higher level of water fluoride. In this case, the confidence interval ranges from 4 to 21 people. It must be remembered that these numbers are found when comparing to a theoretical low level of 0.4 ppm to 1.0 ppm, if the comparison level was lower the numbers needed to harm would be lower.

7.1.2 Multivariate analysis

The results of the multivariate analysis are presented in Table 7.4. All variables included in this model were statistically significant at the 5% level; all other variables which were investigated (see above) showed no statistically significant association at this level.

Table 7.4  Results of the multivariate analysis of the regression of water fluoride level against the proportion of the population with dental fluorosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Parameter</th>
<th>P-value individual parameters</th>
<th>P-values Overall Variables</th>
<th>Coefficient</th>
<th>Variance</th>
<th>Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td>Interception</td>
<td>0.85</td>
<td>-0.069</td>
<td>0.146</td>
<td>0.933 (0.435 to 2.003)</td>
<td></td>
</tr>
<tr>
<td>Fluoride level</td>
<td>Fluoride level (ppm)</td>
<td>0.0001</td>
<td>0.718</td>
<td>0.006</td>
<td>2.050 (1.766 to 2.379)</td>
<td></td>
</tr>
<tr>
<td>Method of assessment</td>
<td>Clinical</td>
<td>0.77</td>
<td>0.123</td>
<td>0.177</td>
<td>0.455 (0.220 to 0.943)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photograph</td>
<td>0.12</td>
<td>1.186</td>
<td>0.580</td>
<td>0.044 (0.007 to 0.275)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>0.0001</td>
<td>2.582</td>
<td>0.432</td>
<td>0.005 (0.000 to 0.125)</td>
<td></td>
</tr>
<tr>
<td>Teeth type</td>
<td>Permanent</td>
<td>0.04</td>
<td>-0.787</td>
<td>0.138</td>
<td>1.131 (0.495 to 2.583)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>0.001</td>
<td>-3.131</td>
<td>0.880</td>
<td>3.274 (0.736 to 14.571)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>0.002</td>
<td>-5.241</td>
<td>2.606</td>
<td>13.218 (3.642 to 47.977)</td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td>Not Stated</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

These results show that the only variables to show a statistically significant association at the 5% level with the prevalence of dental fluorosis were water fluoride level, method of outcome assessment and teeth type. The odds of fluorosis were higher in studies using both a photographic and clinical assessment, compared with studies using a clinical or photographic examination and were slightly
higher in studies using a photographic rather than a clinical assessment (in both high fluoride and low fluoride areas). This may be due to the drying of teeth before photographing them, allowing visualisation of more enamel defects. The odds of fluorosis were higher in permanent than primary teeth, and in studies looking at permanent teeth only compared with those looking at both permanent and primary dentitions. Controlling for these factors led to a small decrease in the between study variance for both the estimates of the intercept and slope. Some examples of the proportion of the population that would be predicted to have dental fluorosis at various levels of the exposures included in the final multivariate model are provided in Table 7.5.

Table 7.5 Multivariate model prediction of proportion of the population that would be expected to have dental fluorosis at various levels of exposure, method of measurement and teeth type

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>% of the population with dental fluorosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2ppm fluoride, identified clinically, both teeth types</td>
<td>2 (0, 11)</td>
</tr>
<tr>
<td>0.4ppm fluoride, identified clinically, both teeth types</td>
<td>3 (1, 17)</td>
</tr>
<tr>
<td>0.7ppm fluoride, identified using photograph, permanent teeth</td>
<td>61 (31, 85)</td>
</tr>
<tr>
<td>1.0ppm fluoride, identified using photograph, permanent teeth</td>
<td>67 (37, 88)</td>
</tr>
<tr>
<td>1.0ppm fluoride, identified using both methods of assessment, both teeth types</td>
<td>44 (12, 81)</td>
</tr>
<tr>
<td>2.0ppm fluoride, identified clinically, permanent teeth</td>
<td>54 (45, 62)</td>
</tr>
</tbody>
</table>

* both teeth types = permanent and primary teeth combined

7.2 Proportion of the population with dental fluorosis of aesthetic concern

7.2.1 Univariate analysis

The results of the model fitted in the univariate analysis are presented in Table 7.6

Table 7.6 Proportion of the population with dental fluorosis of aesthetic concern

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Coefficient</th>
<th>Variance</th>
<th>Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0001</td>
<td>-1.729</td>
<td>0.108</td>
<td>0.177 (0.091 to 0.346)</td>
</tr>
<tr>
<td>Fluoride level</td>
<td>0.0001</td>
<td>0.82985</td>
<td>0.0231</td>
<td>2.293 (1.685 to 3.120)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between study (intercept) Sigma 2u</td>
<td></td>
<td></td>
<td>3.830</td>
<td></td>
</tr>
<tr>
<td>Between study (fluoride level – slope) Sigma 2v</td>
<td></td>
<td>0.634</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariance of intercept and slope Sigma u v</td>
<td></td>
<td>0.113</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This shows that fluoride level has a statistically significant positive association with the prevalence of fluorosis of aesthetic concern. The between study variance in the estimate of the intercept slope of the regression line are higher than they were for the overall fluorosis analysis, indicating greater heterogeneity between studies. Using these model estimates, confidence intervals can be constructed for the proportion of persons in a population with fluorosis for a given level of water fluoridation (see Table 7.7).

Table 7.7 The proportion (%) of the population with dental fluorosis of aesthetic concern at different water fluoride concentrations

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>% of the population affected by fluorosis of aesthetic concern (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>6.3 (3.2, 12.4)</td>
</tr>
<tr>
<td>0.2</td>
<td>6.9 (3.5, 13.1)</td>
</tr>
<tr>
<td>0.4</td>
<td>8.2 (4.2, 14.9)</td>
</tr>
<tr>
<td>0.7</td>
<td>10.0 (5.0, 17.9)</td>
</tr>
<tr>
<td>1</td>
<td>12.5 (7.0, 21.5)</td>
</tr>
<tr>
<td>1.2</td>
<td>14.5 (8.2, 24.4)</td>
</tr>
<tr>
<td>2</td>
<td>24.7 (14.3, 39.4)</td>
</tr>
<tr>
<td>4</td>
<td>63.4 (37.9, 8.3)</td>
</tr>
</tbody>
</table>

This association is illustrated in Figure 7.2.
Figure 7.2  Proportion of the population with dental fluorosis of aesthetic concern by water fluoride level together with the 95% upper and lower confidence limits for the proportion

Figure 7.2 shows an increasing prevalence of fluorosis of aesthetic concern with increasing water fluoride level. The effect that changing the water fluoride level of a low fluoride area with 0.4ppm fluoride in the water supply to an area with 0.7, 1.0 and 1.2ppm in the water supply is shown in Table 7.8.

Table 7.8  Difference in the proportion of the population affected with fluorosis of aesthetic concern comparing a low level of water fluoride to levels around 1ppm

<table>
<thead>
<tr>
<th>Fluoride ppm</th>
<th>Difference in proportions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 v 0.7</td>
<td>2.0 (-6 to 10)</td>
</tr>
<tr>
<td>0.4 v 1.0</td>
<td>4.5 (-4.5 to 13.6)</td>
</tr>
<tr>
<td>0.4 v 1.2</td>
<td>6.5 (-3.3 to 16.2)</td>
</tr>
</tbody>
</table>

The figures shown in Table 7.8 show that the difference between the proportion of the population affected with fluorosis of aesthetic concern at 0.4ppm compared with 0.7ppm is considerably lower than the difference in the proportion comparing 0.4ppm to 1.0ppm and 1.2ppm. Increasing the water fluoride level from 0.4 to 1.0ppm, the level to which water supplies are often artificially fluoridated, would mean that one additional person for every 22 people receiving water fluoridated to this level would have fluorosis of aesthetic concern. However, the confidence limits around this value include infinity, which means that it is possible that there is no risk. This is because the differences in proportions were not statistically significant (the confidence intervals include zero).

### 7.2.2 Multivariate analysis

The multivariate analysis of fluorosis of aesthetic concern is presented in Appendix K because the findings were similar to the findings on the primary analysis of fluorosis, section 7.1.2.

### 7.3 Sensitivity analysis

A sensitivity analysis of the regression analysis was conducted in which all data points above 1.5ppm were removed from the data set. It was suggested that the higher water fluoride levels were forcing the regression line to show a relationship that may not actually exist for the lower levels of fluoride. Restricting the analysis to levels less than 1.5ppm allowed the investigation of any association at these lower levels.
7.3.1 Fluorosis sensitivity analysis

The results of the univariate regression model are presented in Table 7.9.

Table 7.9 Results of the univariate regression of water fluoride level against the proportion of the population with dental fluorosis (sensitivity analysis)

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Coefficient</th>
<th>Variance</th>
<th>Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.01</td>
<td>-0.475</td>
<td>0.031</td>
<td>0.622 (0.437 to 0.885)</td>
</tr>
<tr>
<td>Log fluoride level (centred by adding -0.526051)</td>
<td>0.0001</td>
<td>0.5861</td>
<td>0.0070</td>
<td>1.797 (1.525 to 2.118)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between study (intercept)</td>
<td></td>
<td></td>
<td>2.026</td>
<td></td>
</tr>
<tr>
<td>Between study (fluoride level – slope)</td>
<td></td>
<td></td>
<td>0.349</td>
<td></td>
</tr>
<tr>
<td>Covariance of intercept and slope</td>
<td></td>
<td></td>
<td>-0.338</td>
<td></td>
</tr>
</tbody>
</table>

The model shows similar findings to the previous model (Table 7.1). The log of the odds of the prevalence of dental fluorosis continues to show a linear association with the log of water fluoride level. However, the gradient of the effect is slightly shallower (the increase in odds of fluorosis were 2.05 (95% CI: 1.75 to 2.39) in the first model and 1.80 (95% CI: 1.53 to 2.12) per unit increase of fluoride) in the sensitivity analysis.

Table 7.10 shows the estimates of the proportion (%) of the population with fluorosis at various water fluoride levels predicted by the model.

Table 7.10 Proportion of the population with dental fluorosis by water fluoride level together with the 95% upper and lower confidence limits for the proportion (sensitivity analysis)

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>Proportion (%) of the population affected by fluorosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>18 (12, 26)</td>
</tr>
<tr>
<td>0.2</td>
<td>25 (18, 33)</td>
</tr>
<tr>
<td>0.4</td>
<td>33 (26, 41)</td>
</tr>
<tr>
<td>0.7</td>
<td>41 (33, 49)</td>
</tr>
<tr>
<td>1</td>
<td>46 (37, 55)</td>
</tr>
<tr>
<td>1.2</td>
<td>49 (40, 58)</td>
</tr>
</tbody>
</table>

The proportions of the population predicted to have fluorosis by this model are similar to the initial model in the lower water fluoride levels. However, the confidence intervals are larger. The graphical representation of this model is shown in Figure 7.3.

Figure 7.3 Proportion of the population with dental fluorosis by water fluoride level and predicted 95% confidence limits (sensitivity analysis)
7.3.2 Fluorosis of aesthetic concern sensitivity analysis

The results of the univariate regression model of fluorosis of aesthetic concern are presented in Table 7.11.

Table 7.11 Results of the univariate regression of water fluoride level against the proportion of the population with fluorosis of aesthetic concern (sensitivity analysis)

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Coefficient</th>
<th>Variance</th>
<th>Odds (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0001</td>
<td>-1.953</td>
<td>0.130</td>
<td>0.142 (0.070 to 0.287)</td>
</tr>
<tr>
<td>Fluoride level (centred by subtracting 1.2565)</td>
<td>0.02</td>
<td>0.712</td>
<td>0.083</td>
<td>2.038 (1.159 to 3.583)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between study (intercept)</td>
<td></td>
<td></td>
<td></td>
<td>4.117</td>
</tr>
<tr>
<td>Between study (fluoride level – slope)</td>
<td></td>
<td></td>
<td></td>
<td>0.238</td>
</tr>
<tr>
<td>Covariance of intercept and slope</td>
<td></td>
<td></td>
<td></td>
<td>1.657</td>
</tr>
</tbody>
</table>

Similar to the original model, this model shows that fluoride level is statistically significantly associated with the prevalence of fluorosis of aesthetic concern. Again, the odds are slightly lower in this model, 0.14 (95% CI: 0.07 to 0.29), than in the original model, 0.18 (0.09 to 0.35). The predictions of the new model are given in Table 7.12.

Table 7.12 The proportion (%) of the population with dental fluorosis of aesthetic concern at different water fluoride concentrations

<table>
<thead>
<tr>
<th>Fluoride level</th>
<th>% of the population affected by fluorosis of aesthetic concern (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>6 (2, 14)</td>
</tr>
<tr>
<td>0.2</td>
<td>6 (3, 14)</td>
</tr>
<tr>
<td>0.4</td>
<td>7 (3, 15)</td>
</tr>
<tr>
<td>0.7</td>
<td>9 (4, 17)</td>
</tr>
<tr>
<td>1</td>
<td>10 (5, 20)</td>
</tr>
<tr>
<td>1.2</td>
<td>12 (6, 22)</td>
</tr>
</tbody>
</table>

The point estimates here are slightly lower than in the original model (Table 7.6), but there is more uncertainty reflected in the larger confidence intervals. The graphical representation of the model is show in Figure 7.4.

Figure 7.4 Proportion of the population with fluorosis of aesthetic concern by water fluoride level and predicted 95% Confidence Intervals
### 7.4 Studies that met inclusion criteria but were not included in the main analysis

The studies included in Table 7.13 were not included in the main analysis for the reasons outlined in the table. The conclusions of these studies appear to be compatible with the results of the main analysis of an increase in dental fluorosis with increased water fluoride concentration, so that their exclusion does not materially affect the result.

#### Table 7.13 Studies that met inclusion criteria but were not included in the main analysis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Reason for exclusion</th>
<th>Author’s conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhagan (1996)</td>
<td>Dental fluorosis</td>
<td>No separate results provided for control area – aggregate data only</td>
<td>The intensity of dental fluorosis is related to the concentration of fluoride in the water</td>
</tr>
<tr>
<td>Dissanayake (1979)</td>
<td>Dental fluorosis</td>
<td>The levels of fluoride in the exposed groups cover very wide ranges (0.3-3.8 and 0.3-4.6), which are very close to the levels of the control groups (&lt; 0.2). These data can thus not be analysed in a meaningful way together with the other studies looking at fluorosis.</td>
<td>Author does not make any conclusions regarding the incidence of dental fluorosis. Results indicate a considerably higher incidence of fluorosis in the areas with the higher ranges of fluoride concentrations in the water supplies</td>
</tr>
<tr>
<td>Forsman (1977)</td>
<td>Dental fluorosis</td>
<td>Different age groups are examined for the different fluoride exposure groups and so the results are not comparable between study areas</td>
<td>A greater proportion of children were affected by fluorosis in the higher fluoride area (2.75ppm) and fluorosis was also more severe in this area compared to the control areas (&lt;1.5ppm)</td>
</tr>
<tr>
<td>Hellwig (1985)</td>
<td>Dental fluorosis</td>
<td>Children from naturally fluoridated areas combined with children from areas which changed from a low-fluoride supply to an optimally fluoridated supply 2 years prior to the examination– a significant proportion of the exposed group would not have been exposed to fluoride for enough time for a noticeable effect to have occurred</td>
<td>The incidence and severity of dental fluorosis was higher in the fluoridated areas compared to the control area</td>
</tr>
<tr>
<td>Larsen (1987)</td>
<td>Dental fluorosis</td>
<td>Measures of fluorosis are presented graphically for each tooth type. From these figures it is not possible to obtain an accurate reading.</td>
<td>The prevalence of dental fluorosis increases with the age during which the individual tooth is formed. The concentration of fluoride in the drinking water influenced the occurrence of fluorosis by resulting in a steeper profile of the prevalence from lower incisor to second molars rather than by increasing the prevalence for all teeth.</td>
</tr>
<tr>
<td>Latham (1967)</td>
<td>Dental fluorosis, nail mottling and prevalence of goitre</td>
<td>The results are not broken down as much as the water fluoride levels, giving very wide ranges of fluoride levels in some of the areas for which results are presented. All the areas are fluoridated at above 1ppm and some with fluoride levels as high as 45.5ppm</td>
<td>Author does not specifically relate results to water fluoride content of the area – he comments generally on the results seen in the whole sample studied, as all areas are exposed to comparatively high levels of fluoride. The incidence of dental fluorosis was high in all areas (&gt;82%), as was the percentage of people with mottled nails (&gt;26%), and the prevalence of goitre (12-41%). As these results are not specifically related to the water fluoride level and there was no control area it is difficult to link these findings to the water fluoride levels.</td>
</tr>
<tr>
<td>Author (Year)</td>
<td>Outcome</td>
<td>Reason for exclusion</td>
<td>Author’s conclusions</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Opinya (1991)</td>
<td>Dental fluorosis</td>
<td>Exposed area had fluoride level of 9ppm – considerably above level that would be encountered in artificially fluoridated area. Fluorosis data presented graphically for tooth type, not possible to obtain accurate data from the graphs.</td>
<td>The incidence and severity of fluorosis was greater in the high fluoride area compared to the control area.</td>
</tr>
<tr>
<td>Teng (1996)</td>
<td>Dental fluorosis</td>
<td>Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis.</td>
<td>Index of children’s dental fluorosis has shown a decreased trend since the fluoride level of the water has been reduced.</td>
</tr>
<tr>
<td>Gopalakrishnan (1999)</td>
<td>Dental fluorosis</td>
<td>Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis.</td>
<td>Dental fluorosis is related to the high fluoride content of drinking water.</td>
</tr>
<tr>
<td>Morgan (1998)</td>
<td>Dental fluorosis and childhood behaviour problems</td>
<td>Children classified according to Dean’s classification for fluorosis and then fluoride exposure examined. Childhood behaviour problems classified according to dental fluorosis levels not water fluoride levels.</td>
<td>The use of supplemental fluoride prior to age 3 was found to be a risk factor for dental fluorosis. No significant association was found between fluoride history variables in aggregate (including water fluoride level) and dental fluorosis. Dental fluorosis was not significantly associated with behaviour problems in the children studied.</td>
</tr>
</tbody>
</table>

### 7.5 Prevalence of fluorosis over time

As with caries, the introduction of fluoride toothpaste in the 1970’s could play a role in increasing the prevalence or degree of fluorosis occurring. Figure 7.5 presents the data on percent prevalence of fluorosis from 32 studies divided into before 1975 (23) and after 1985 (9), to allow sufficient time for fluorosis development after exposure to fluoridated toothpaste. These studies were conducted in nine countries (Australia, Canada, Finland, Ireland, Italy, New Zealand, Sweden, Britain, and the USA). Figure 7.5 is the main analysis measure of fluorosis; there were not enough data points to assess fluorosis of aesthetic concern. The bars represent different ranges of water fluoride (natural or artificial).
Figure 7.5 shows similar patterns and prevalence of fluorosis both before 1975 and after 1985. An increase in the prevalence of fluorosis over time was not seen in this analysis of water fluoridation studies. While this finding is counterintuitive, no explanation is evident from these data. However, the measure of use of other fluoride sources was very crude.

Table 7.14 Studies that controlled for the effects of other fluoride use.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Sources of fluoride</th>
<th>Other variables included in model</th>
<th>Classification of fluorosis</th>
<th>Results: Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ismail (1990)</td>
<td>Fluoride tablet use</td>
<td>Type of school, city, sex, age</td>
<td>TSIF&gt;=1</td>
<td>F tablet use = 1.70 (1.28, 2.27)</td>
</tr>
<tr>
<td>Riordan (1991)</td>
<td>Fluoride tablet use (short, medium and long term) versus no fluoride tablet use, likes toothpaste, started toothpaste &lt; 1 year and 1-3 years versus &gt;3 years, and swallowed toothpaste</td>
<td>Resident in fluoridated area for 1.2-4 years or 2.5-4 years versus &lt;1 year</td>
<td>TF score &gt;0</td>
<td>F tablets short: 1.55 (0.54, 4.42) F tablets medium: 0.87 (0.30, 2.52) F tablets long: 4.63 (1.97, 10.90) Likes toothpaste: 1.27 (0.75, 2.15) Started toothpaste &lt;1 yr: 1.35 (0.72, 2.55) Started toothpaste 1-3 yr: 1.20 (0.63, 2.29) Swallowed toothpaste 1.02 (0.71, 1.45)</td>
</tr>
<tr>
<td>Szpunar (1988)</td>
<td>Fluoride rinse, use of fluoride supplements, dental attendance, age started brushing</td>
<td>Town, male education, age</td>
<td>Categorised as having fluorosis at TSIF&gt;=1</td>
<td>Use of fluoride supplements, dental attendance, age started brushing not associated with fluorosis (no results presented). Fluoride rinse use = 1.57 (1.02, 2.41)</td>
</tr>
<tr>
<td>Brothwell (1999)</td>
<td>Fluoride supplements, fluoridated mouthwash, age parent brushed with fluoride paste,</td>
<td>Water fluoride level, breast feeding, highest level of education, household income</td>
<td>Categorised as having fluorosis at TSIF&gt;=1</td>
<td>Fluoride supplements: 1.93 (1.02-3.62) Fluoride mouthwash: 2.73 (1.06-7.05) Age parent brushed: 0.93 (0.40-2.19)</td>
</tr>
<tr>
<td>Butler (1985)</td>
<td>Fluoride toothpaste, number of fluoride treatments, fluoride drops</td>
<td>Home air conditioning, race, total dissolved solids and zinc</td>
<td>CFI (Dean’s community fluorosis index) stratified by exposure.</td>
<td>Use of fluoride toothpaste/drops and number of fluoride treatments almost identical in those that did and did not develop moderate fluorosis, therefore not included in multivariate analysis.</td>
</tr>
<tr>
<td>Heller (1997)</td>
<td>Fluoride drops, fluoride tablets, professional F treatment, school fluoride rinses</td>
<td>Water fluoride level, age</td>
<td>Fluorosis categorised as Dean’s score of very mild or greater</td>
<td>Fluoride drops: 1.49 (1.11, 1.99) Fluoride tablets: 1.20 (0.96, 1.49) Professional F: 1.05 (0.85, 1.28) School fluoride rinse: 1.14 (0.84, 1.55)</td>
</tr>
<tr>
<td>Angelllo (1999)</td>
<td>Frequency of tooth brushing</td>
<td>Univariate analysis results presented</td>
<td>CFI (Dean’s community fluorosis index) stratified by exposure.</td>
<td>Results presented as CFI (sd): Tooth-brushing &lt; 1 day: 0.15 (0.31) &gt; 1 day: 0.13 (0.37) No significant association so not included in multivariate analysis.</td>
</tr>
<tr>
<td>Kumar (1999)</td>
<td>Fluoride tablets and early brushing</td>
<td>Race and water fluoride level</td>
<td>Compared very mild or worse with normal.</td>
<td>Early brushing: 2.0 (1.2, 3.3) Fluoride tablet: 2.9 (1.3, 4.7) All compared to no fluoride exposure from any of these sources or from water fluoride.</td>
</tr>
<tr>
<td>Skotowsk i (1995)</td>
<td>Fluoride supplements, age started brushing, total toothpaste usage in 8 years, mouth rinse usage</td>
<td>Drinking water fluoride</td>
<td>Dental fluorosis present if received TSIF score&gt;=1.</td>
<td>Fluoride supplement use, mouth rinse use and age started brushing not significant in univariate analysis so not included in multivariate analysis. Fluoride exposure from toothpaste significant in univariate and multivariate analysis (adjusted OR not presented)</td>
</tr>
</tbody>
</table>
7.6 Possible confounding factors

There are likely to be many possible confounding factors in cross-sectional studies of dental fluorosis. Temperature and altitude are two that are frequently mentioned, but not controlled for in these studies. People living in climates with a higher mean temperature drink more water, thus being exposed to more total fluoride. Higher altitude has also been thought to be associated with the development of fluorosis, although the mechanism for this is unclear. Fluorosis can be difficult to distinguish from other developmental defects of enamel.

7.6.1 Studies which adjusted for the possible confounding effect of other sources of fluoride

Nine studies of the association between fluorosis and water fluoridation used multiple logistic regression analysis to control for the possible confounding effects of other sources of fluoride. The results of these analyses and the variables controlled for in the regression analysis are presented in Table 7.14. All results presented as adjusted odds ratios with 95% confidence intervals. These studies found mixed results, with no definite association between the other sources of fluoride studied and fluorosis.

7.7 Potential publication bias

The data were analysed in such a way that an measure of effect was not produced for each individual study thus it was not possible to investigate publication bias using standard methods.

7.8 Discussion

Fluorosis was the most widely and frequently studied of all the possible adverse effects considered. The fluorosis studies used cross-sectional designs, with a few before-after designs (again using different groups of people at each time point). The mean validity score was only 2.8 out of 8 and all but one of the studies were of evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for potential confounding factors, or reducing potential observer bias were infrequently undertaken. Seventy-two of 88 studies did not use any form of blinding of the assessor, and 50 of 88 did not control for confounding factors, other than by simple stratification by age or sex.

The primary fluorosis analysis was based on prevalence of ‘fluorosed’ people, including any degree of fluorosis. A conservative approach to defining fluorosis was used for this analysis, in that the ‘questionable’ category in Dean’s index was counted as fluorosis. Because there is evidence that very mild forms of fluorosis are not concerning to people (indeed some even preferred photographs of mildly fluorosed teeth) a secondary analysis assessed the prevalence of fluorosis of ‘aesthetic concern’.

With both methods of measuring the prevalence of fluorosis, a significant dose-response relationship was identified through the univariate regression analysis (Tables 7.1 and 7.6; Figures 7.1 and 7.2). The prevalence of fluorosis at a water fluoride level of 1.0ppm was estimated to be 48% (95% CI 40 to 57) for any fluorosis and 12.5% (95% CI 7.0, 21.5) for fluorosis of aesthetic concern. The numbers of additional people who would have to be exposed to water fluoride levels of 1.0 or 1.2ppm for one additional person to develop fluorosis of any level were quite low, 5 or 6 when comparing to a theoretical low fluoride level of 0.4ppm (Table 7.3). For fluorosis of aesthetic concern to occur in one additional person, however, the number was 22 at 1ppm, but the 95% CI included infinity (Table 7.8).

The multivariate analysis of fluorosis took into account variables potentially contributing to the heterogeneity between studies. This analysis found a statistically significantly higher risk in children with permanent teeth, compared with primary teeth or both types (Table 7.4). The multivariate analysis of fluorosis of aesthetic concern confirmed these findings (Appendix K). A sensitivity analysis limiting the range of water fluoride levels entered into the model did not alter the findings in any meaningful way.

The estimated NNT for one extra child to be caries-free (Chapter 4) was seven (95% CI 5 to 10), while the NNH for fluorosis is six (95% CI 4 to 21), with approximately a quarter of these being of aesthetic concern. These estimates are based on comparisons of specific levels of water fluoridation (e.g. < 0.7 ppm vs 0.7 to 1.2 ppm for caries, and 0.4 ppm vs 1.0 ppm for fluorosis). The numbers would change if different levels of fluoridation were compared.
Objective 4: Does water fluoridation have negative effects?

8. BONE FRACTURE AND BONE DEVELOPMENT PROBLEMS

A total of 29 studies of the effect of exposure to fluoridated water on bones met inclusion criteria. Among these were four prospective cohort studies, six retrospective cohort studies, 15 ecological studies, one case-control study, one study which used both a case-control and ecological design and two studies which met the inclusion criteria but was not included in the analysis for the reasons outlined in section 8.1. These papers studied a variety of fracture sites as well as slipped epiphysis in older children and young adults, and otosclerosis (malformation of bones in the ear). Hip fracture was included or was the only outcome in 18 studies. Details of baseline information and results from each study can be found in tables in Appendix C.

All but one of the studies looking at the association of water fluoride level with bone fractures were of evidence level C. The other study was of evidence level B, the average checklist score was 3.4 out of 8 (range 1.5 to 6.0). Only four of the 25 studies used a prospective study design, none used any form of blinding and only one study conducted a baseline examination prior to the introduction of fluoridation. The two lowest scoring studies did not address or control for any possible confounding factors. There were two case-control studies, both of which were of evidence level C, scoring 3.5 and 4 out of a possible 9 on the validity checklist.

Tables 8.1 to 8.4 present summaries of the findings of all eligible bone fracture studies included in the review, organised by fracture site or bone development problem. A point estimate of the size of the effect, the statistical significance of this measure and the study validity scores are also reported. In all calculations made by the review team, the area with the water fluoride level closest to 1.0 ppm was chosen and compared to the area with the lowest water fluoride level reported.

A forest plot of all the bone studies showing the measures of effect and their 95% confidence intervals was produced (Figure 8.1) for all studies that provided sufficient data to calculate a relative risk, odds-ratio or standardised rate-ratio and its 95% confidence interval. The majority of the measures of effect and their confidence intervals were distributed around 1, the line of no effect for related measures (suggesting no association), with no obvious outliers noted. The studies included in the forest plots differ from one another in a number of respects. Data are presented for both sexes, for different age groups and for different fracture sites (colour coded), using crude or adjusted outcomes and a variety of study designs.

In Figure 8.1, point estimates to the left of the vertical line indicate fewer fractures with exposure to fluoridated water, while those to the right side of the line indicate more fractures.
Figure 8.1 Bone fracture incidence (Measure of effect estimate and 95% CI)
Table 8.1 Effect of water fluoridation on hip fracture

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Sex</th>
<th>RR (95% CI)</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cauley (1995)</td>
<td>65+</td>
<td>Women</td>
<td>0.44 (0.1, 1.9)*</td>
<td>6.0</td>
</tr>
<tr>
<td>Jacqmin-Gadda (1998)</td>
<td>65+</td>
<td>Both</td>
<td>2.43 (1.1, 5.3)*</td>
<td>5.5</td>
</tr>
<tr>
<td>Sowers (1991)</td>
<td>20-35</td>
<td>Women</td>
<td>1.68 (0.07, 40.1)</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>55-80</td>
<td>Women</td>
<td>8.18 (0.46, 146.6)</td>
<td></td>
</tr>
<tr>
<td>Li (1999)</td>
<td>50+</td>
<td>Both</td>
<td>0.99 (0.3, 3.2)</td>
<td>5.0</td>
</tr>
<tr>
<td>Jacqmin-Gadda (1995)</td>
<td>65+</td>
<td>Both</td>
<td>1.86 (1.0, 3.4)*</td>
<td>5.0</td>
</tr>
<tr>
<td>Sowers (1991)</td>
<td>55-80</td>
<td>Women</td>
<td>0.67 (0.5, 0.8)*</td>
<td>4.5</td>
</tr>
<tr>
<td>Li (1999)</td>
<td>50+</td>
<td>Women</td>
<td>0.99 (0.3, 3.2)</td>
<td>5.0</td>
</tr>
<tr>
<td>Jacqmin-Gadda (1995)</td>
<td>50+</td>
<td>Women</td>
<td>1.08 (0.9, 1.3)*</td>
<td>4.5</td>
</tr>
<tr>
<td>Kurttio (1999)</td>
<td>50+</td>
<td>Men</td>
<td>0.91 (0.7, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Hillier (2000)</td>
<td>50+</td>
<td>Both</td>
<td>1 (0.7, 1.5)*</td>
<td>4.0</td>
</tr>
<tr>
<td>Lehmann (1998)</td>
<td>35+</td>
<td>Women</td>
<td>0.83 (0.7, 0.9)</td>
<td>3.8</td>
</tr>
<tr>
<td>Danielson (1992)</td>
<td>65+</td>
<td>Women</td>
<td>1.27 (1.1, 1.5)*</td>
<td>3.7</td>
</tr>
<tr>
<td>Jacobsen (1992)</td>
<td>65+</td>
<td>Women</td>
<td>1.08 (1.06, 1.10)</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1.17 (1.13, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Cooper (1990)</td>
<td>45+</td>
<td>Both</td>
<td>1 (0.7, 1.5)*</td>
<td>3.3</td>
</tr>
<tr>
<td>Suarez-Almazor (1993)</td>
<td>45-64</td>
<td>Women</td>
<td>0.85 (0.7, 1.03)</td>
<td>3.0</td>
</tr>
<tr>
<td>Madans (1983)</td>
<td>65+</td>
<td>Women</td>
<td>0.96 (0.9, 1.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45-64</td>
<td>Men</td>
<td>1.13 (1.0, 1.27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1.07 (1.087, 1.32)</td>
<td></td>
</tr>
<tr>
<td>Simonen (1985)</td>
<td>50+</td>
<td>Women</td>
<td>0.7 (0.6, 0.9)*</td>
<td>2.5</td>
</tr>
<tr>
<td>Korns (1969)</td>
<td>50+</td>
<td>Men</td>
<td>0.4 (0.3, 0.6)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40+</td>
<td>Men</td>
<td>1.75 (0.6, 4.9)</td>
<td>2.5</td>
</tr>
<tr>
<td>Karagas (1996)</td>
<td>65+</td>
<td>Women</td>
<td>No association</td>
<td>1.5</td>
</tr>
<tr>
<td>Arnal (1986)</td>
<td>50+</td>
<td>Both</td>
<td>0.96 (0.8, 1.2)</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1 (0.9, 1.1)*</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* = unadjusted relative risk; RR = adjusted relative risk (see data extraction tables for further details of adjustment made in each study); 1 in the Sowers study there were no cases in the control group and so a Haldane approximation was used to estimate the relative risk.

A total of 18 studies (see Table 8.1) investigated the association of hip fracture with water fluoride level, making 30 analyses (e.g. men only, women only, both). Fourteen analyses found the direction of the association between water fluoridation and hip fracture to be positive (decreased hip fracture with increased water fluoride level). Five were statistically significant associations. Thirteen analyses found the direction of association to be negative (increased hip fracture), but only four of these found a statistically significant effect. Three additional analyses did not find any association. Three of the 18 studies found the direction of association positive in women but negative in men and one study found a negative effect in women and a positive effect in men.

There were no definite patterns of association for any of the fractures, for example, with all studies finding a positive effect for a particular fracture. A total of 30 analyses were conducted in 12 studies (see Table 8.2). Overall 14 analyses found the direction of association of water fluoridation and bone fracture to be negative (more fractures), of which one was statistically significant. Thirteen analyses found the direction of association to be positive (fewer fractures), of which one was statistically significant and two did not report variance data. Three analyses found no association. The two studies that found statistically significant effects were Li (1999), which found a small protective effect in both sexes for all fractures, while Karagas (1996) found a small negative effect in men for increased risk of fracture of the humerus. While both of these analyses were statistically significant, the 95% CI only just excluded 1.0.
### Table 8.2 Effect of water fluoridation on other fractures

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Fracture</th>
<th>Age</th>
<th>Sex</th>
<th>RR (95% CI)</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sowers (1991)</td>
<td>All fractures</td>
<td>20-35</td>
<td>Women</td>
<td>1.81 (0.5, 8.2)*</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55-80</td>
<td>Women</td>
<td>2.11 (1.0, 4.4)*</td>
<td></td>
</tr>
<tr>
<td>Jacqmin-Gadda (1995)</td>
<td>All fractures</td>
<td>65+</td>
<td>Both</td>
<td>0.98 (0.8, 1.2)*</td>
<td>5.0</td>
</tr>
<tr>
<td>Li (1999)</td>
<td></td>
<td>65+</td>
<td>Both</td>
<td>0.69 (0.5, 0.9)</td>
<td>5.0</td>
</tr>
<tr>
<td>Avorn (1986)</td>
<td></td>
<td>65+</td>
<td>Women</td>
<td>1.2 (1.0, 1.5)</td>
<td>3.1</td>
</tr>
<tr>
<td>Kroger (1994)</td>
<td></td>
<td>47-56</td>
<td>Women</td>
<td>1.14 (0.9, 1.4)</td>
<td>2.8</td>
</tr>
<tr>
<td>McClure (1944)</td>
<td></td>
<td>19-23</td>
<td>Men</td>
<td>0.78 (0.6, 1.0)</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-17</td>
<td>Men</td>
<td>0.95 (0.7, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Kroger (1994)</td>
<td>Ankle</td>
<td>47-56</td>
<td>Women</td>
<td>1.14 (0.7, 1.9)</td>
<td>2.8</td>
</tr>
<tr>
<td>Karagas (1996)</td>
<td></td>
<td>65+</td>
<td>Women</td>
<td>1 (0.9, 1.1)*</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1.01 (0.9, 1.2)*</td>
<td></td>
</tr>
<tr>
<td>Bernstein (1966)</td>
<td>Collapsed vertebrae</td>
<td>45+</td>
<td>Women</td>
<td>0.26</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45+</td>
<td>Men</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Karagas (1996)</td>
<td>Distal forearm</td>
<td>65+</td>
<td>Women</td>
<td>Author states no association</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1.16 (1.0, 1.3)*</td>
<td></td>
</tr>
<tr>
<td>Karagas (1996)</td>
<td>Humerus</td>
<td>65+</td>
<td>Women</td>
<td>Author states no association</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>Men</td>
<td>1.23 (1.1, 1.4)*</td>
<td></td>
</tr>
<tr>
<td>Phipps (1999)</td>
<td>Non-hip</td>
<td>65+</td>
<td>Both</td>
<td>1.05 (0.7, 1.5)*</td>
<td>5.5</td>
</tr>
<tr>
<td>Cauley (1995)</td>
<td>Non-spine</td>
<td>65+</td>
<td>Women</td>
<td>0.73 (0.5, 1.1)*</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>Women</td>
<td>0.96 (0.8, 1.1)*</td>
<td>4.3</td>
</tr>
<tr>
<td>Cauley (1995)</td>
<td>Osteoporotic</td>
<td>65+</td>
<td>Women</td>
<td>0.74 (0.5, 1.2)*</td>
<td>6.0</td>
</tr>
<tr>
<td>Kroger (1994)</td>
<td>Other</td>
<td>47-56</td>
<td>Women</td>
<td>1.03 (0.8, 1.3)</td>
<td>2.8</td>
</tr>
<tr>
<td>Cauley (1995)</td>
<td>Vertebral</td>
<td>65+</td>
<td>Women</td>
<td>1.83 (0.6, 4.7)*</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>Women</td>
<td>0.74 (0.6, 1.0)*</td>
<td>4.3</td>
</tr>
<tr>
<td>Cauley (1995)</td>
<td>Wrist</td>
<td>65+</td>
<td>Women</td>
<td>0.95 (0.4, 2.3)*</td>
<td>6.0</td>
</tr>
<tr>
<td>Phipps (1999)</td>
<td></td>
<td>65+</td>
<td>Women</td>
<td>1.3 (1.0, 1.7)*</td>
<td>4.3</td>
</tr>
<tr>
<td>Kroger (1994)</td>
<td></td>
<td>47-56</td>
<td>Women</td>
<td>1.3 (1.0, 2.1)</td>
<td>2.8</td>
</tr>
<tr>
<td>Korns (1969)</td>
<td></td>
<td>40+</td>
<td>Men</td>
<td>0.4 (0.0, 2.1)</td>
<td>2.5</td>
</tr>
<tr>
<td>Korns (1969)</td>
<td></td>
<td>40+</td>
<td>Women</td>
<td>0.95 (0.5, 1.7)</td>
<td></td>
</tr>
</tbody>
</table>

* = unadjusted relative risk; RR = adjusted relative risk (see data extraction tables for further details of adjustment made in each study)

Three studies were included which examined the effects of water fluoridation on outcomes related to bone development (Table 8.3). Both studies of otosclerosis reported a beneficial effect of fluoridation, although no statistical analysis was presented. The study of slipped epiphyses found the direction of association to be positive (a protective effect) in girls and negative (increased risk) in boys, but neither of these was statistically significant at the 5% level.

### Table 8.3 Effect of water fluoridation on bone development disorders

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Bone Development Defect</th>
<th>Age</th>
<th>Sex</th>
<th>RR (95% CI)</th>
<th>Validity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karjalainen (1982)</td>
<td>Otosclerosis</td>
<td>All</td>
<td>Women</td>
<td>0.93</td>
<td>3.7</td>
</tr>
<tr>
<td>Daniel (1969)</td>
<td></td>
<td>All</td>
<td>Both</td>
<td>0.26</td>
<td>2.5</td>
</tr>
<tr>
<td>Kelsey (1971)</td>
<td>Slipped epiphysis</td>
<td>&lt;25</td>
<td>Women</td>
<td>0.65 (0.4, 1.2)</td>
<td>3.8</td>
</tr>
</tbody>
</table>
8.1 Studies that met inclusion criteria but were not included in the main analysis

Two studies met inclusion criteria but were not included in the main analysis. Details of the studies and the reason for not including them in the main analysis are provided in Table 8.4.

Table 8.4 Studies which met inclusion criteria but were not included in the main analysis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Reason for exclusion</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sowers (1986)</td>
<td>Bone fracture</td>
<td>The levels of fluoride in the control groups were similar to artificial levels of fluoridation. Women were classified according to water fluoride and calcium concentration. The high fluoride group (F level = 4ppm) was low in calcium and the lower fluoride groups (F level = 1pm) had very high and high levels of calcium in the water. This was likely to confound any association observed between water fluoride level and fracture incidence.</td>
<td>Intake of water providing ~4ppm of fluoride does not decrease fracture rate in young adult women or in postmenopausal women in a population-based setting. There was a history of more frequent fracture among women in the community with greater fluoride in drinking water as compared to women in the other 2 communities. Substantial fluoride intake may magnify the need for adequate dietary calcium and vitamin D intake, particularly in premenopausal women.</td>
</tr>
<tr>
<td>Horne (2000)</td>
<td>Bone fracture</td>
<td>Only the abstract was available. This did not provide sufficient details for inclusion of this study in the main analysis. The authors compared hip fractures and knee DJD joint replacements among those &gt;65 years for 1991-1996 in a community with fluoridated water and 2 without. Directly standardised age-adjusted rates were calculated, these are not presented in the abstract. Only reports on one age-group which showed a significant association, results of other age-groups not presented and so it is not possible to draw conclusions from the limited results presented.</td>
<td>An association between fluoride and DJD of the knee was not supported, while a trend in the females for hip fracture was observed.</td>
</tr>
</tbody>
</table>

The level of water fluoride concentration examined in the Sowers (1986) study was higher than the level to which water supplies would be artificially fluoridated. The authors did not appear to find any significant association of fracture with water fluoride concentration, despite the possible confounding effect of the difference in calcium concentrations between the study areas. Full details of the Horne (2000) study were not available and the results presented in the abstract were insufficient for inclusion in the review or to draw any conclusions as to the results of this study.

8.2 Potential confounding factors

The incidence of hip fracture is strongly associated with age and sex, thus any study investigating the incidence of hip fracture should control for these variables. Other factors that may confound the association between water fluoride content and fracture incidence include body mass index (BMI), ethnicity, calcium intake, certain drugs, non-water fluoride exposure and the menopausal status of women. Of the 27 studies included in the analysis of water fluoridation and fracture incidence, 10 studies presented crude results only (some of these stratified on age and sex), 12 presented adjusted effect measures such as relative risks and odds ratios, and five studies presented standardised results. Of these, six studies failed to control for the effect of any possible confounding factors. Five studies presented results separately by sex and three studies controlled for age only (one of these controlled for age by only selecting people above a certain age). Five studies included only people within a certain age grouping and presented results by sex. Four studies controlled for the effects of both age and sex. Three studies controlled for age, sex and BMI and four studies controlled for other variables in addition to these three variables.
8.3 Meta-regression

Heterogeneity was investigated using the Q statistic and found to be significant thus a meta-regression was carried out to investigate possible sources of heterogeneity between studies. Variables that may account for the differences in effect-size seen between studies were included in the regression model. The natural log of the outcome measure (relative risk, odds ratio or standardised rate ratio) was included as the dependent variable in the regression analysis. The results were then exponentiated to make the results more easy to interpret (see below for further details). The Haldane approximation was used to estimate variance where there were no cases in one of the groups. This involves adding 0.5 to the cells in a contingency table in which there are no cases.

Several of the studies included in the meta-regression contribute more than one estimate to the analysis. Some studies looked at different age groups or stratified results on sex and many of the studies looked at more than one fracture site. It has been assumed in this analysis that these subgroups of people are independent and hence each estimate has been treated as though it came from a separate study. The potential limitations of including these estimates in the same regression are discussed in section 12.6.

Continuous measures were centred on the mean (the mean value of each variable was subtracted from each of the individual measures), before including them in the regression model. Centring continuous variables in this way results in the constant (or intercept) of the regression model pertaining to the pooled estimate of the mean difference when the explanatory variable takes its mean value.

A univariate analysis was undertaken in which each of the variables was included individually in the regression model with the log of the relative risk, odds ratio or standardised rate ratio of the incidence of fracture in the fluoridated compared to the control study area. For studies that presented results for more than two study areas the comparison included in this analysis is the summary measure which compares the area with the fluoride level closest to 1ppm to the area with the lowest water fluoride level. If studies presented summary age-adjusted estimates in addition to age specific measures this estimate was included in the analysis, for studies in which no overall estimate was available age-specific or crude estimates were included.

A measure of the between study variance (heterogeneity) remaining after the variables included in the model had been accounted for was calculated using restrictive maximum likelihood estimation. Variables which showed a significant association with the outcome variable at the 15% significance level (p<0.15) in the univariate analysis were included in the multivariate analysis. The multivariate analysis was carried out using a step-down analysis in which each variable was included in the initial model. Variables were dropped one by one, with the variable that showed the least evidence of a significant association dropped first, until only variables which showed a significant association at the 5% level were included in the analysis. The analysis was repeated using step-up analysis to confirm the results of the step-down analysis. As a further exploratory analysis study validity was forced into the regression model as the effect of study validity was considered to be very important in these studies of variable quality.

8.3.1 Univariate analysis

The results of the univariate analysis are shown in Table 8.5. A total of 55 measure of effect estimates from 20 studies were included in the analysis.

At the 15% significance level the following variables showed a significant association with the summary measure: study duration and measure of exposure. These variables were included in the multivariate analysis. The model in which no variables (other than the outcome measure) were included shows the pooled estimate of the summary measure to be 1.00 (95% CI: 0.94, 1.06). This is the same as the measure that would be produced by a standard meta-analysis. The between study variance (heterogeneity) was investigated and found to be significant (Q statistic = 197 on 54 degrees of freedom, p<0.001). This pooled estimate suggests that there is no association between water fluoridation and fracture incidence. However, because of the significant heterogeneity this value should be interpreted with extreme caution.
Table 8.5 Results of the univariate meta-regression analysis for bone fractures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category (number of analyses)</th>
<th>Constant (95% CI)</th>
<th>p-value of constant</th>
<th>Co-efficient (95% CI)</th>
<th>p-value of co-efficient</th>
<th>Between study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variables (pooled estimate)</td>
<td></td>
<td>1.00 (0.94, 1.06)</td>
<td>0.926</td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;35 (4)</td>
<td>0.89 (0.69, 1.14)</td>
<td>0.345</td>
<td>1.00 (0.73, 1.38)</td>
<td>0.983</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>35+ (6)</td>
<td></td>
<td></td>
<td>1.21 (0.90, 1.62)</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50+ (10)</td>
<td></td>
<td></td>
<td>0.91 (0.68, 1.21)</td>
<td>0.502</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65+ (27)</td>
<td></td>
<td></td>
<td>1.20 (0.92, 1.56)</td>
<td>0.170</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS (2)</td>
<td></td>
<td></td>
<td>1.10 (0.71, 1.71)</td>
<td>0.660</td>
<td></td>
</tr>
<tr>
<td>Study duration*</td>
<td>&lt;5 (17)</td>
<td>1.04 (0.96, 1.13)</td>
<td>0.357</td>
<td>1.03 (0.91, 1.17)</td>
<td>0.649</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>5-10 (19)</td>
<td></td>
<td></td>
<td>0.69 (0.56, 0.84)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 (4)</td>
<td></td>
<td></td>
<td>0.90 (0.77, 1.04)</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>Measure of* exposure</td>
<td>% exposed (10)</td>
<td>1.07 (0.95, 1.20)</td>
<td>0.271</td>
<td>0.92 (0.80, 1.07)</td>
<td>0.276</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Years of exposure (10)</td>
<td></td>
<td></td>
<td>0.85 (0.69, 1.04)</td>
<td>0.118</td>
<td></td>
</tr>
<tr>
<td>Highest estimate of water fluoride level</td>
<td>Low (2)</td>
<td>1.30 (0.84, 1.99)</td>
<td>0.236</td>
<td>0.76 (0.20, 1.17)</td>
<td>0.214</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Optimum (49)</td>
<td></td>
<td></td>
<td>1.68 (0.75, 3.75)</td>
<td>0.205</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Relative risk (48)</td>
<td>0.98 (0.91, 1.05)</td>
<td>0.512</td>
<td>1.19 (0.93, 1.52)</td>
<td>0.178</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio (5)</td>
<td></td>
<td></td>
<td>1.15 (0.87, 1.53)</td>
<td>0.335</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standardised rate ratio (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was an adjusted results presented?</td>
<td>No (18)</td>
<td>0.97 (0.86, 1.09)</td>
<td>0.594</td>
<td>1.04 (0.91, 1.20)</td>
<td>0.567</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Yes (37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the result adjusted for bmi?</td>
<td>No (45)</td>
<td>0.99 (0.93, 1.14)</td>
<td>0.855</td>
<td>1.03 (0.84, 1.27)</td>
<td>0.771</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>Yes (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the result adjusted for age?</td>
<td>No (20)</td>
<td>0.97 (0.86, 1.10)</td>
<td>0.652</td>
<td>1.03 (0.90, 1.19)</td>
<td>0.634</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>Yes (34)</td>
<td></td>
<td></td>
<td>1.03 (0.61, 1.74)</td>
<td>0.919</td>
<td></td>
</tr>
<tr>
<td>Fracture site</td>
<td>Hip (27)</td>
<td>0.97 (0.89, 1.06)</td>
<td>0.549</td>
<td>1.03 (0.85, 1.25)</td>
<td>0.759</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Wrist (5)</td>
<td></td>
<td></td>
<td>1.22 (0.90, 1.64)</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ankle (3)</td>
<td></td>
<td></td>
<td>1.05 (0.81, 1.36)</td>
<td>0.695</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal forearm (1)</td>
<td></td>
<td></td>
<td>1.19 (0.81, 1.75)</td>
<td>0.374</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humerus (2)</td>
<td></td>
<td></td>
<td>1.23 (0.90, 1.69)</td>
<td>0.196</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-hip (1)</td>
<td></td>
<td></td>
<td>1.08 (0.65, 1.79)</td>
<td>0.771</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-spine (2)</td>
<td></td>
<td></td>
<td>0.90 (0.65, 1.25)</td>
<td>0.538</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoporotic (1)</td>
<td></td>
<td></td>
<td>0.76 (0.42, 1.38)</td>
<td>0.369</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (1)</td>
<td></td>
<td></td>
<td>1.06 (0.68, 1.64)</td>
<td>0.800</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertebral (2)</td>
<td></td>
<td></td>
<td>0.85 (0.55, 1.32)</td>
<td>0.472</td>
<td></td>
</tr>
<tr>
<td>Was the result adjusted for sex?</td>
<td>No (5)</td>
<td>0.99 (0.81, 1.21)</td>
<td>0.917</td>
<td>1.01 (0.82, 1.24)</td>
<td>0.938</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Yes (49)</td>
<td></td>
<td></td>
<td>1.01 (0.58, 1.76)</td>
<td>0.970</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male (8)</td>
<td>1.00 (0.89, 1.11)</td>
<td>0.948</td>
<td>1.00 (0.86, 1.15)</td>
<td>0.957</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Female (31)</td>
<td></td>
<td></td>
<td>1.02 (0.82, 1.27)</td>
<td>0.832</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both (16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validity*</td>
<td>3.65</td>
<td>0.99 (0.93, 1.06)</td>
<td>0.846</td>
<td>0.99 (0.94, 1.04)</td>
<td>0.748</td>
<td>0.030</td>
</tr>
</tbody>
</table>

* Included in multivariate analysis

8.3.2 Multivariate analysis

The multivariate model shows the effect of each variable controlled for the possible effects of the other variables included in the model. The results of the multivariate analysis are shown in Table 8.6. Study duration was the only variable to show a significant association at the 5% level with the summary measures (relative risk, odds ratio or standardised measure of effect) for the association of water fluoridation with bone fracture incidence. This variable reduced the between study variance from 0.029 to 0.018 in the final model. The analysis was repeated using a step-up analysis, this produced a similar model. This shows that the direction of association (non-significant) is negative (more fractures) for studies that last for less than five years and between five and 10 years and positive (fewer fractures) for studies in which duration is not stated. A statistically significant positive
association was seen in studies that lasted for longer than 10 years, meaning that fewer fractures occur in fluoridated areas compared to non-fluoridated areas if they are studied longer than 10 years. Study validity did not show a statistically significant association with the measure of effect at the 5% level, and was not included in the multivariate model. The model with validity forced in is presented in Appendix L.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Co-efficient (95% CI)</th>
<th>p-value</th>
<th>Between study variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td></td>
<td>1.04 (0.96, 1.13)</td>
<td>0.357</td>
<td>0.018</td>
</tr>
<tr>
<td>Study duration</td>
<td>&lt;5 (17)</td>
<td>1.03 (0.91, 1.17)</td>
<td>0.649</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-10 (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 (4)</td>
<td>0.69 (0.56, 0.84)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not stated (15)</td>
<td>0.90 (0.77, 1.04)</td>
<td>0.160</td>
<td></td>
</tr>
</tbody>
</table>

8.4 Publication bias

A funnel plot to assess potential publication bias could not be constructed for bone fracture studies. The funnel plot graphs sample size versus measure of effect. The studies included in the meta-regression did not provide sufficient data on the sizes of the populations studied to make a plot. Because the measures of effect reported in these studies were distributed around 1, the line of no effect for relative measures, it would be unlikely that a funnel plot would be helpful in detecting potential publication bias. One additional study of osteoporotic bone fracture by Sowers, which included measurement of duration of residence, individual drinking water fluoride and serum fluoride levels, has been conducted. Communication with the author indicates that no association was found. However, while this study has been submitted to the Journal of Bone and Mineral Research, it has not yet been published.

8.5 Discussion

There were 29 studies included on bone fracture and bone development problems. Other than fluorosis, bone effects (not including bone cancers) were the most studied potential adverse effect. These bone studies also had low validity (3.4 out of 8) with all but one study being evidence level C. These studies included both retrospective and prospective cohort designs, some of which included appropriate analyses controlling for potential confounding factors. Observer bias could potentially play a role in bone fracture, depending on how the study is conducted.

The graph of estimates of association for all bone fracture studies (Figure 8.1) shows that the individual estimates of effect lie very close to a relative risk of 1.0. Most of the confidence intervals cross 1.0 (statistically non-significant). The only confidence intervals that do not include 1.0 (statistically significant) are evenly distributed, five indicating an increased risk of fracture and four indicating a decreased risk. The meta-regression showed that the pooled estimate of the association of bone fracture with water fluoridation was 1.00 (0.94, 1.06), however due to the significant heterogeneity between studies this value should be interpreted with extreme caution. The meta-regression showed that the only variable (out of 30 total) associated with the summary measure at the 5% significance level was study duration. Factors which would be expected to show an association with fracture incidence, such as fracture site, age and sex, were not associated with water fluoride level at the 5% significance level in either the univariate or multivariate models. This adds support to the result suggested by the pooled estimate of no association between water fluoridation and fracture incidence.

The evidence on bone fracture can be classified into hip fracture and other sites as there were a greater number of studies on hip fracture than any other site. Using a qualitative method of analysis, there is no clear association of hip fracture with water fluoridation (Table 8.5). Of 18 studies, three showed a statistically significant benefit, and two showed statistically significant harm, and three showed no effect of water fluoridation on hip fracture. One study found no cases of hip fracture in the low fluoride group, indicating harm from water fluoridation. The evidence on other fractures is similar (Table 8.2); of 30 study comparisons one found statistically significant benefit, one found statistically significant harm and three found no effect. The evidence on other bone outcomes was extremely limited. A negative association was suggested in the risk of slipped epiphysis in boys, but this finding was not statistically significant.
Objective 4: Does water fluoridation have negative effects?

CANCER STUDIES

A total of 26 studies examining the association between exposure to fluoridated water and cancer incidence and mortality met inclusion criteria; 10 before-after studies, 11 ecological studies, three case-control studies and two studies which met inclusion criteria but were not included in the main analysis for the reasons outlined in Table 9.4. These papers studied incidence and mortality from a variety of cancers, including all cancers, osteosarcoma, bone cancer, thyroid cancer and other site-specific cancers. Details of baseline information and results from each study can be found in tables in Appendix C.

Five of the studies of the association of cancer with water fluoride level achieved an evidence level of B (evidence of moderate quality, moderate risk of bias), the rest were of evidence level C (lowest quality of evidence, high risk of bias). The average validity checklist score was 3.8 out of 8 (range 2.8-4.8). For the three case-control studies the average score was 4.6 out of 9 (range 3.5 to 6.0). None of the included studies had a prospective follow-up or reported any form of blinding.

Analyses of cancer incidence and mortality data were identified for a variety of different cancers. The results of the studies considering all-cause cancer incidence and mortality and those that looked at osteosarcoma or bone and joint cancers, and thyroid cancer are presented below. All-cause cancer incidence is presented, as this is the outcome most commonly presented by the studies. The results of bone-cancer studies are also presented because if fluoride is linked to a site-specific cancer incidence, it is biologically plausible that this site would be affected because fluoride is taken up by bones. It has been suggested that fluoride may have an effect on the thyroid gland and for this reason studies which looked at cancer of the thyroid gland were also considered separately.

9.1 Cancer mortality from all causes

Table 9.1 shows the effect of fluoridation on all cause cancer incidence and mortality, a point estimate for this association, the measure used, and a measure of the significance of the association. Where studies presented an adjusted measure this is presented. For ecological or cohort studies that did not present an adjusted relative risk but did provide details on the number of cases and population at risk, an unadjusted relative risk was calculated. For studies that used an ecological or cohort study design that presented standardised mortality or incidence ratios (SMR/SIRs) the mean difference of the SMR/SIR was calculated together with the 95% confidence interval. For studies that used a before-after study design and presented relative risks or rate-ratios for two points in time the ratio of the summary measure comparing the final survey to the baseline survey was calculated. For studies that used a before-after study design and presented SMR/SIRs for both points in time, the difference of the change in SMR/SIRs from baseline to final survey between the fluoridated and control area was calculated. For studies that present a difference measure (e.g. mean difference) a negative result suggests a positive effect of fluoridation, and a positive result suggests a negative effect of fluoridation (i.e. greater cancer incidence in the fluoride group compared with the control group). For ratio measurements a ratio less than 1 suggests a positive effect of fluoridation and a ratio greater than one suggests a negative effect. If the confidence interval for this measure includes 1 or if the p-value is less than 0.05 then this suggests a statistically significant difference. In all calculations made by the review team, the area with the water fluoride level closest to 1.0 ppm was chosen and compared to the area with the lowest water fluoride level reported.

All cause cancer incidence and mortality was considered as an outcome in 10 studies, in which 22 analyses were made. Of these, 11 found the direction of association of water fluoridation and cancer to be positive (fewer cancers) and 9 found the direction of association to be negative (more cancers), 2 studies found no association of water fluoride exposure and cancer. One study (Lynch, 1985) found a statistically significant negative effect in 2 of the 8 sub-groups investigated; this was not confirmed when other sub-groups were considered (Appendix C). One study (Smith, 1980) found a statistically significant positive effect. There does not appear to be any association between validity and the direction of the association of water fluoride exposure and cancer incidence. Of the two studies with the highest validity scores (4.8 and 4.2) one found a statistically significant positive association (Smith, 1980) the other found a mixed effect (Lynch 1985); some analyses showed a statistically significant
negative effect and others showing statistically non-significant associations in both directions. Overall these studies do not appear to show any association between overall cancer incidence and water fluoride exposure.

### Table 9.1 Effect of fluoridation on cancer incidence and mortality

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Sex</th>
<th>Summary measure</th>
<th>Results (95% CI)</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (1980)</td>
<td>All ages</td>
<td>Both</td>
<td>Mean difference of change in SMRs</td>
<td>-4.4 (-7.5, -1.3)</td>
<td>4.8</td>
</tr>
<tr>
<td>Lynch (1985)</td>
<td>All ages</td>
<td>Male</td>
<td>Mean difference in SIRs</td>
<td>9.00 (p&lt;0.001) 2.10 (p=0.592) -6.80 (p=0.057) -1.10 (p=0.500) 5.9 (p&lt;0.001) 2.3 (p=0.565) 0.1 (p=1.000) 2 (p=0.630)</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chilvers (1983)</td>
<td>All ages</td>
<td>Both</td>
<td>Mean difference of change in SMRs</td>
<td>-0.1 (-3.8, 3.6)</td>
<td>3.8</td>
</tr>
<tr>
<td>Hoover (1976)</td>
<td>All ages</td>
<td>Male</td>
<td>Mean difference in SMRs</td>
<td>0 (-3.5, 3.5) 0 (-3.8, 3.8)</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chilvers (1985)</td>
<td>All ages</td>
<td>Male</td>
<td>Mean difference in SMRs</td>
<td>-0.49 (-5.7, 4.8) -1.56 (-7.4, 4.3)</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodall (1980)</td>
<td>Not stated</td>
<td>Male</td>
<td>Ratio of crude rate-ratios</td>
<td>0.85</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Raman (1977)</td>
<td>All ages</td>
<td>Male</td>
<td>Mean difference of change in SMRs</td>
<td>6.9</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Cook-Mozaffari (1981)</td>
<td>All ages</td>
<td>Male</td>
<td>Ratio of Rate-Ratios</td>
<td>0.99</td>
<td>3.3</td>
</tr>
<tr>
<td>Richards (1979)</td>
<td>All ages</td>
<td>Both</td>
<td>Mean difference in SMRs</td>
<td>-3.3 (-18.7, 12.1)</td>
<td>3.1</td>
</tr>
<tr>
<td>Schlesinger (1956)</td>
<td>All ages</td>
<td>Male</td>
<td>Ratio of crude rate ratios</td>
<td>0.6</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>1.01</td>
<td></td>
</tr>
</tbody>
</table>

### 9.1.1 Studies of 20 US cities

Several studies presented analyses of data for the same set of cities in the USA, 10 fluoridated and 10 non-fluoridated cities (Table 9.2). These cities were originally selected and analysed by Yiamouyiannis (1977). The other studies present a re-analysis of the data included in this study, although some have selected slightly different years to investigate or have obtained data through different sources. All studies used before-after study designs comparing cancer incidence before and after the introduction of water fluoridation in 10 of the 20 study areas.

In the original study, Yiamouyiannis found a positive association between increased water fluoride and cancer incidence (more cancers). This study has been criticised for not taking into account demographic differences between the two groups of cities at baseline and inadequately accounting for changes in age (e.g., finer age bands) and gender structure between the baseline and final study years. Yiamouyiannis grouped men and women and whites and non-whites together into broad age groups (0-24, 25-44, etc) for the calculation of mortality ratios. The data show that the proportion of the populations that were non-white and over 65 years of age increased more rapidly in the fluoridated than in the non-fluoridated areas (Doll 1977).

The other studies use standardisation to control for age, sex and ethnic group. These studies did not find an association between cancer mortality and water fluoridation in the selected cities. Yiamouyiannis criticised the analysis used by Doll (1977) because the data used, supplied by the National Cancer Institute (NCI) contained a data transcription error which was repeated in the paper (Yiamouyiannis, 1977). Yiamouyiannis also argued that the analysis was inappropriate because 90-95% of the available data were omitted and that the selection of the year 1970 as one of the study years was inappropriate as fluoridation of the control group had already started. This had in fact only been started in two of the cities shortly (months) before the 1970 data were collected. Doll justified the
choice of 1970 as a census year for which more accurate population data were available. Smith (1980) used the corrected NCI figures in a similar analysis and also failed to detect any association between water fluoridation and cancer mortality in the selected cities.

For the analysis presented here, the results of the four studies which analysed data for the same 20 US cities are presented together in Table 9.2. The study which scored the highest on the validity checklist, and did not include the error in the NCI data (Smith, 1980) is included in the main analysis in Table 9.1.

Table 9.2  Studies which present analyses of the same set of data for 20 cities in the USA

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Sex</th>
<th>Summary measure</th>
<th>Results (95% CI)</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doll (1977)</td>
<td>NS</td>
<td>Both</td>
<td>Mean difference of change in SMRs</td>
<td>-7.0 (-10.6, -3.4)</td>
<td>4.8</td>
</tr>
<tr>
<td>Chilvers (1982)</td>
<td>NS</td>
<td>Both</td>
<td>Mean difference of change in SMRs</td>
<td>-1.8 (-7.9, 4.2)</td>
<td>4.8</td>
</tr>
<tr>
<td>Smith (1980)</td>
<td>All ages</td>
<td>Both</td>
<td>Mean difference of change in SMRs</td>
<td>-4.4 (-7.5, -1.3)</td>
<td>4.8</td>
</tr>
<tr>
<td>Yiamouyiannis (1977)</td>
<td>0-24</td>
<td>Both</td>
<td>Ratio of crude rate ratios</td>
<td>1.01</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>25-44</td>
<td></td>
<td></td>
<td>1.03</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>45-64</td>
<td></td>
<td></td>
<td>1.03</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.2 Osteosarcoma and bone cancer

Table 9.3 shows the association of osteosarcoma, bone and joint cancer incidence and mortality with water fluoride level, a point estimate of variance for this association, the measure used, and a measure of the significance of the association. Where studies presented an adjusted measure this is presented. For studies that did not present an adjusted relative risk but did provide details on the number of cases and population at risk, an unadjusted relative risk was calculated.

Table 9.3 Association of osteosarcoma, bone and joint cancer incidence and mortality with water fluoride level

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer</th>
<th>Summary measure</th>
<th>Results (95% CI)</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinlen (1975)</td>
<td>All ages</td>
<td>Both</td>
<td>Bone</td>
<td>Mean difference in SMRs</td>
<td>6 (-50.8, 62.8)</td>
<td>4.0</td>
</tr>
<tr>
<td>Hoover (1976)</td>
<td>All ages</td>
<td>Male</td>
<td>Bone</td>
<td>Mean difference in SMRs</td>
<td>0 (-35.9, 35.9)</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>20 (-22.6, 62.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoover (1991)</td>
<td>All ages</td>
<td>Both</td>
<td>Bone and joint</td>
<td>Mean difference of change in SIRs</td>
<td>1 (-30.2, 32.2)</td>
<td>3.3</td>
</tr>
<tr>
<td>Mahoney (1991)</td>
<td>&lt;30</td>
<td>Male</td>
<td>Bone</td>
<td>Crude RR</td>
<td>0.93</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Female</td>
<td></td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>Male</td>
<td></td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>Female</td>
<td></td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moss (1995)</td>
<td>Not stated</td>
<td>Both</td>
<td>Osteosarcoma</td>
<td>OR</td>
<td>1.0 (0.6, 1.5)</td>
<td>6.0</td>
</tr>
<tr>
<td>Gelberg (1995)</td>
<td>&lt;24</td>
<td>Osteosarcoma</td>
<td>OR</td>
<td>2.07 (0.5, 8.0)</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;24</td>
<td>OR</td>
<td>1.84 (0.8, 4.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hrudey (1990)</td>
<td>All ages</td>
<td>Osteosarcoma</td>
<td>Crude RR</td>
<td>0.93 (0.6, 1.6)</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Hoover (1991)</td>
<td>All ages</td>
<td>Osteosarcoma</td>
<td>Mean difference of change in SIRs</td>
<td>-11 (-44.6, 22.6)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>McGuire (1991)</td>
<td>0-40</td>
<td>Both</td>
<td>Osteosarcoma</td>
<td>OR</td>
<td>0.33 (0.0, 2.5)</td>
<td>3.5</td>
</tr>
<tr>
<td>Mahoney (1991)</td>
<td>&lt;30</td>
<td>Male</td>
<td>Osteosarcoma</td>
<td>Crude RR</td>
<td>0.98</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Female</td>
<td></td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>Male</td>
<td></td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>Female</td>
<td></td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohn (1992)</td>
<td>0-20</td>
<td>Male</td>
<td>Osteosarcoma</td>
<td>Crude RR</td>
<td>3.4 (1.4, 8.1)</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>1.0 (0.3, 3.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Four studies considered the association of bone related cancer and water fluoride exposure, performing eight analyses. Of these, the direction of association of water fluoridation and bone cancer was found to be positive in three, negative in four and one did not detect a relationship. None of the studies found a statistically significant association, however one study (Mahoney 1991) contributed five of the nine analyses with no variance data.

Seven studies of osteosarcoma, presenting 12 analyses were included. Of these, the direction of association between water fluoridation and osteosarcoma incidence or mortality was found to be positive (fewer cancers) in seven, negative (more cancers) in three, and two found no relationship. Of the six studies that presented variance data, one (Cohn 1992) found a statistically significant association between fluoridation and increased prevalence of osteosarcoma in males. This study however, also had the lowest validity score, 2.5 out of 8. One study (Mahoney 1991) contributed four of the 12 analyses but did not provide variance data.

9.3 Cancer of the thyroid gland

Two studies (Kinlen 1975, Hoover 1976) investigated the association of water fluoride level with cancer of the thyroid gland. Both studies used indirect standardisation to control for the effects of age and sex and did not find any association between water fluoride level and thyroid cancer (Appendix C).

9.4 Studies that met the inclusion criteria but were not included in the main analysis

The studies in table 9.4 met the inclusion criteria but were not included in the main analysis for the reasons outlined in the table. Both of these studies appear to confirm the results of the main analysis: a lack of association between water fluoride content and cancer incidence and mortality.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Reason</th>
<th>Authors Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoover (1990)</td>
<td>Cancer Mortality</td>
<td>Non-fluoridated areas grouped together with areas fluoridated within the past five years.</td>
<td>The relative risk of death from cancers of the bones and joints was the same after 20-35 years of fluoridation as it was in the years immediately preceding fluoridation. A similar lack of relationship to timing of fluoridation was noted for the incidence of bone and joint cancers and osteosarcomas. The relative risk of developing these cancers 20 or more years after fluoridation was lower than the risk associated with less than five years of fluoridation among both males and females. For no type of malignancy was there consistent evidence of a relationship with patterns of fluoride. In a study of over 2300000 cancer deaths in fluoridated counties across the US, and over 125000 incident cancer cases in fluoridated counties covered by two population based cancer registries, no trends in cancer risk that could be ascribed to the consumption of fluoridated drinking water could be identified.</td>
</tr>
<tr>
<td>Swanberg (1953)</td>
<td>Cancer Mortality</td>
<td>Cancer mortality compared between fluoridated area and the whole of the US - includes areas with fluoride in the water supplies and so not a suitable control area</td>
<td>The death rate from cancer in the study area decreased during the study period whereas the death rate from cancer in the whole of the US (the control area) increased over the same period.</td>
</tr>
</tbody>
</table>

9.5 Possible confounding factors

There is a dramatic increase in cancer with age and a considerable difference in cancer mortality between men and women and among different ethnic groups, thus even small differences in the age, sex and ethnic structure of a population can lead to noticeable differences in cancer incidence. Any study looking at the association of cancer with different exposures should therefore control for these confounding factors in the analysis. There are numerous other factors that may also lead to
differences in cancer incidence between populations if the exposure of populations differ, for example, smoking, social class, diet and environmental factors, including exposure to other sources of fluoride. Of the 26 cancer studies in the main analysis, 12 used standardisation (11 used the indirect and one the direct method) to control for age and sex (some studies presented results separately by sex) and four of these also controlled for ethnic group. One study presented an age adjusted rate, and five studies presented crude data only. Of the three case-control studies, one presented a crude odds ratio matched on age, gender and county of residence, one presented an odds ratio with cases and controls matched on sex and year of birth (age). The third matched cases and controls on age, sex and race and then presented an odds ratio adjusted for population size, age radiation exposure and gender.

9.6 Discussion
The evidence of the effect of water fluoridation on cancer was of the highest quality available under Objective 4 (3.8 out of 8 compared with a mean of 2.7 for other possible negative effects) but was still only low to moderate. Twenty-one of the 26 studies presented are from the lowest level of evidence (level C) with the highest risk of bias. While prospective study designs may be more difficult to conduct in cancer studies due to long incubation periods and rarity of some cancers, they are possible. Blinding of outcome assessment to exposure is certainly possible in such studies, for example outcomes assessed using published sources could blind investigators to fluoride levels in the study areas.

There is no clear picture of association between water fluoridation and overall cancer incidence and mortality (Table 9.1). Whilst there were 11 analyses that found the direction of association of water fluoridation and cancer to be positive (fewer cancers), a further nine analyses found a negative direction of association (more cancers), and two studies found no effect. Only two studies found statistical significance, both suggesting an association in different directions. One of these studies contained eight analyses of which only two found a statistically significant adverse effect of water fluoridation.

While a broad number of cancers were represented in the included studies, osteosarcoma, bone/joint and thyroid cancers were of particular concern due to fluoride uptake by bone and thyroid. Again, no clear association between water fluoridation and increased incidence or mortality was apparent. Of eight analyses from the six studies of osteosarcoma and water fluoridation reporting variance data, none found statistically significant differences. Thyroid cancer was also considered but only two studies examined this and neither found a statistically significant association with water fluoride level.

The findings of cancer studies were mixed, with small variations on either side of no effect. Individual cancers examined were bone cancers and thyroid cancer, where once again no clear pattern of association was seen. Overall, from the research evidence presented no association was detected between water fluoridation and mortality from any cancer, or from bone or thyroid cancers specifically.
Objective 4: Does water fluoridation have negative effects?

10. OTHER POSSIBLE NEGATIVE EFFECTS

A total of 33 studies of the association of water fluoridation with other possible negative effects were included in the review. There were six before and after studies, one retrospective cohort study, 12 ecological studies, five cross sectional, one case control study and eight studies which met inclusion criteria but were not included in the main analysis for reasons outlined below (Table 10.3 and section 10.2). These studies examined a variety of different outcomes including Down's syndrome, mortality, senile dementia, goitre and IQ. Details of baseline information and results from each study can be found in tables in Appendix C. Two studies (Briner 1966 and Schatz 1976) presented data from the same two cities in Chile from similar time periods. To avoid duplication, only the Schatz study is presented in the tables below, but both studies are included in the data tables in Appendix C. Although some authors (Spittle 1993) have reported cases of hypersensitivity to fluoridated water, no studies meeting the inclusion criteria were found.

The quality of these studies was generally low; all studies were of evidence level C (lowest quality of evidence, high risk of bias). The average validity checklist score was 2.7 out of 8 (range 1.5-4.5). None of the studies had a prospective follow up or incorporated any form of blinding. Whilst the one case control study (Dick, 1999) achieved a validity checklist score of 7 out of 9, it should be noted that this study was also of evidence level C.

Table 10.1 shows the effect of water fluoridation on all potential adverse outcomes (other than fluorosis, bone fracture and cancer) reported in the studies included. A point estimate for this association, the measure used and a measure of the significance of the association is presented. Where studies reported an adjusted measure, this is presented. For studies that did not present an adjusted relative risk but did provide details on the number of people studied and population at risk, an unadjusted relative risk was calculated from these data.

For studies that present a difference measure (e.g. mean difference) a negative result suggests a benefit of fluoridation, and a positive result suggests harm from fluoridation (i.e. greater cancer incidence in the fluoride group compared with the control group). For ratio measurements a ratio less than 1 suggests a benefit of fluoridation and a ratio greater than one suggests harm. If the confidence interval for this measure includes 1 or if the p-value is less than 0.05 then this suggests a statistically significant difference.

Only three studies showed a statistically significant effect at the 5% level. Forbes (1997), found a statistically significant negative effect of water fluoride on Alzheimer’s disease (increased incidence) and a statistically significant positive effect on impaired mental functioning (decreased incidence). Erickson (1976) found a statistically significant positive association with congenital malformations in one of two sets of data but not in the other. Lin (1991) found statistically significant negative association of combined low-iodine/high fluoride with goitre and mental retardation. Age at menarche, anaemia during pregnancy and sudden infant death syndrome (SIDS) did not show statistically significant associations with water fluoride exposure. The direction of association of primary degenerative dementia (Still 1980) and cognitive impairment (Jacqmin-Gadda 1994) with water fluoridation was positive (fewer cases) but no measure of the statistical significance of this effect was provided. Skeletal fluorosis and IQ both found the direction of association with water fluoride to be negative, but again no measure of the statistical significance of this association was presented.

Five studies examined the association between all cause mortality and water fluoride exposure. Three studies found the direction of association of water fluoridation and mortality to be negative (more deaths), one found the direction of association to be positive (fewer deaths) and one found no association. Once again, no measures of the statistical significance of these associations were provided. However, for two of the studies that found a negative direction of association, the point estimate was 1.01, which is unlikely to have reflected a statistically significant effect. Three studies examined the association between infant mortality and water fluoride level. All three studies found a negative direction of association, but again no measure of the statistical significance of this association was presented and so it is difficult to draw conclusions from these results.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Age</th>
<th>Sex</th>
<th>Summary measure</th>
<th>Results (95% CI)</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forbes (1997)</td>
<td>Alzheimer's disease</td>
<td>76</td>
<td>Both</td>
<td>Adjusted odds ratio</td>
<td>1.22 (1.0-1.5)</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Impaired mental functioning</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.3-0.9)</td>
<td></td>
</tr>
<tr>
<td>Still (1980)</td>
<td>Primary degenerative dementia</td>
<td>&gt;55</td>
<td>Both</td>
<td>Crude RR</td>
<td>0.18</td>
<td>3.0</td>
</tr>
<tr>
<td>Jacqmin-Gadda (1994)</td>
<td>Cognitive impairment</td>
<td>&gt;= 65</td>
<td>Both</td>
<td>Crude RR</td>
<td>0.93</td>
<td>4.5</td>
</tr>
<tr>
<td>Griffith (1963)</td>
<td>Anaemia during pregnancy</td>
<td>Not stated</td>
<td>Women</td>
<td>Rate difference</td>
<td>2.03 (-5.0-9.0)</td>
<td>2.3</td>
</tr>
<tr>
<td>Farkas (1983) Erickson (1976)</td>
<td>Age at menarche</td>
<td>7-18</td>
<td>Girls</td>
<td>Mean difference</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>0.08 (p&gt;0.05)</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Down's syndrome</td>
<td></td>
<td></td>
<td></td>
<td>0.95 (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.16 (p&gt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96 (p&gt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Erickson (1980)</td>
<td>Congenital malformations</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>1.00 (0.9-1.1)</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Down's syndrome</td>
<td></td>
<td></td>
<td></td>
<td>0.93 (0.7, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Berry (1958)</td>
<td>Down's syndrome</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>0.84-1.48</td>
<td>1.8</td>
</tr>
<tr>
<td>Needleman (1974)</td>
<td>Down's syndrome</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>1.14</td>
<td>2.0</td>
</tr>
<tr>
<td>Rapaport (1957)**</td>
<td>Down's syndrome</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Rapaport (1963)</td>
<td>Down's syndrome</td>
<td></td>
<td>Both</td>
<td>Crude RR</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Infant mortality</td>
<td></td>
<td></td>
<td></td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Dick (1999)</td>
<td>Sudden Infant Death Syndrome</td>
<td>Not stated</td>
<td>Both</td>
<td>Odds ratio</td>
<td>1.19 (0.8, 1.7)</td>
<td>7 (of 9)</td>
</tr>
<tr>
<td>Overton (1954)</td>
<td>Infant mortality</td>
<td></td>
<td>Both</td>
<td>Difference in RR</td>
<td>0.06</td>
<td>2.8</td>
</tr>
<tr>
<td>Erickson (1978)</td>
<td>Mortality</td>
<td>All</td>
<td>Both</td>
<td>Adjusted rate-ratio</td>
<td>1.01</td>
<td>3.8</td>
</tr>
<tr>
<td>Hagan (1954)</td>
<td>Mortality</td>
<td>Not stated</td>
<td>Both</td>
<td>Adjusted rate-ratio</td>
<td>1.01</td>
<td>3.5</td>
</tr>
<tr>
<td>Rogot (1978)</td>
<td>Mortality</td>
<td>Not stated</td>
<td>Both</td>
<td>Difference in RR</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>Schatz (1976)*</td>
<td>Mortality</td>
<td>Not stated</td>
<td>Both</td>
<td>Difference in RR</td>
<td>-0.1</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Infant mortality</td>
<td>Not stated</td>
<td>Both</td>
<td>Difference in RR</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Weaver (1944)</td>
<td>Mortality</td>
<td>Not stated</td>
<td>Both</td>
<td>Difference in RR</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>Zhao (1996)</td>
<td>IQ</td>
<td>7-14</td>
<td>Both</td>
<td>Mean difference</td>
<td>-7.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Lin (1991)</td>
<td>IQ</td>
<td>7-14</td>
<td>Not stated</td>
<td>Mean difference</td>
<td>-6</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Mental retardiation</td>
<td>7-14</td>
<td>Not stated</td>
<td>Crude RR</td>
<td>1.6 (1.15, 2.34)</td>
<td></td>
</tr>
<tr>
<td>Jolly (1971)</td>
<td>Skeletal fluorosis</td>
<td>Not stated</td>
<td>Both</td>
<td>Increased prevalence of skeletal fluorosis at higher fluoride concentrations</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Gedalia (1963)</td>
<td>Goitre</td>
<td>7-18</td>
<td>Female</td>
<td>Crude RR</td>
<td>0.16-1.80</td>
<td>2.5</td>
</tr>
<tr>
<td>Jooste (1999)</td>
<td>Goitre</td>
<td>6.12 &amp; 15</td>
<td>Both</td>
<td>Crude RR</td>
<td>0.3-1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Lin (1991)</td>
<td>Goitre</td>
<td>7-14</td>
<td>Not stated</td>
<td>Crude RR</td>
<td>1.11 (1.04, 1.20)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Briner (1966) reported data from the same areas and some of the same years but is not presented here because Schatz reported more years and included infant mortality.

** Multiple areas studied, for details on see Appendix C

Six studies looked at the association between Down’s syndrome and water fluoride level. Three studies found a negative direction of association (Needleman 1974, Rapaport 1957, Rapaport 1963), one found a positive direction of association, one found no association (Berry 1958) and the other found a positive direction of association for one set of data and a negative direction of association for the other. None of the three studies that found a negative direction of association presented any measure of statistical significance. The one study that found a positive direction of association
(Erickson 1980) did present variance data and failed to find a statistically significant association. The study that found a positive direction of association in one set of data and a negative direction of association in the other did not find a statistically significant association in either direction (Erickson 1976).

10.1 Possible confounding factors

All the studies looking at other possible negative effects used study designs that measured population rather than individual exposures to fluoridated water, and because of this they are susceptible to confounding by exposure. If the populations being studied differed in respect to other factors that are associated with the outcome under investigation, then the outcome may differ between these populations leading to an apparent association with water fluoride level. Which factors may act as confounding factors depends on the outcome under investigation and will thus differ for all the different outcomes discussed above. Nineteen analyses looking at other possible negative effects discussed potential confounding factors (Table 10.2). Twelve of these analyses did not control for any of these confounding factors in the results presented.

Table 10.2 Other possible negative effects associated with water fluoride and the confounding factors controlled for in the analysis.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Confounding factors discussed in study</th>
<th>Controlled for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forbes (1997)</td>
<td>Alzheimer’s disease</td>
<td>Water quality variables</td>
<td>Yes</td>
</tr>
<tr>
<td>Still (1980)</td>
<td>Primary degenerative dementia</td>
<td>Chloride, magnesium and calcium content of water</td>
<td>No</td>
</tr>
<tr>
<td>Griffith (1963)</td>
<td>Anaemia during Pregnancy</td>
<td>Parity and stage of pregnancy</td>
<td>No</td>
</tr>
<tr>
<td>Dick (1999)</td>
<td>Sudden Infant Death Syndrome</td>
<td>Age, region, sex, time, season, gestation, ethnicity, etc</td>
<td>Yes</td>
</tr>
<tr>
<td>Erickson (1976)</td>
<td>Down’s syndrome</td>
<td>Maternal age, white births only</td>
<td>Yes</td>
</tr>
<tr>
<td>Erickson (1980)</td>
<td>Congenital malformations</td>
<td>Maternal age, white births only</td>
<td>No</td>
</tr>
<tr>
<td>Needleman (1974)</td>
<td>Down’s syndrome</td>
<td>Maternal age</td>
<td>No</td>
</tr>
<tr>
<td>Rapaport (1957)</td>
<td>Down’s syndrome</td>
<td>Maternal age</td>
<td>No</td>
</tr>
<tr>
<td>Rapaport (1963)</td>
<td>Down’s syndrome</td>
<td>Maternal age effect of other minerals in water, iron, magnesium, manganese calcium</td>
<td>No</td>
</tr>
<tr>
<td>Overton (1954)</td>
<td>Infant mortality</td>
<td>Ethnicity, social and economic conditions</td>
<td>No</td>
</tr>
<tr>
<td>Erickson (1978)</td>
<td>Mortality</td>
<td>Age, sex and ethnicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Hagan (1954)</td>
<td>Mortality</td>
<td>Age, sex and ethnicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Rogot (1978)</td>
<td>Mortality</td>
<td>Age, sex and ethnicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Schatz (1976)</td>
<td>Mortality</td>
<td>Soil and climate</td>
<td>No</td>
</tr>
<tr>
<td>Weaver (1944)</td>
<td>Mortality</td>
<td>Age, sex and area compatibility</td>
<td>No</td>
</tr>
<tr>
<td>Zhao (1996)</td>
<td>IQ</td>
<td>Educational level of parents</td>
<td>No</td>
</tr>
<tr>
<td>Jolly (1971)</td>
<td>Skeletal fluorosis</td>
<td>Sex</td>
<td>Yes</td>
</tr>
<tr>
<td>Jooste (1999)</td>
<td>Goitre</td>
<td>Use of iodised salt, height, weight, urinary, water, &amp; salt levels</td>
<td>No</td>
</tr>
<tr>
<td>Gedalia (1963)</td>
<td>Goitre</td>
<td>Iodine water level</td>
<td>No</td>
</tr>
</tbody>
</table>

For Down’s syndrome, maternal age is of particular importance as a possible confounding factor because the incidence of Down’s syndrome is associated with maternal age. This means that if the average maternal age of the fluoridated population is higher than that of the non fluoridated population, an association with water fluoridation would most likely be found. All but one of the six Down’s syndrome studies considered the effects of maternal age, however only two of these studies attempted to control for this possible confounding factor. The two studies by Erickson (1976, 1980) included white births only and presented results separately for five-year maternal age groups and one of these studies (1976) presented age-adjusted rates. Both of these studies found a non-significant association of water fluoride level with Down’s syndrome at the 5% significance level.

Rapaport (1957) did not control for the effects of confounding factors but did look at the difference in maternal age between the two study areas. He found that maternal age was higher in the low fluoride areas than the high fluoride areas, this would be expected to lead to a higher rate of Down’s syndrome.
in these areas when in fact the reverse was found. Rapaport (1963) also considered maternal age and found that the number of Down’s syndrome births to mothers over the age of 40 was greater in the fluoride areas than the low-fluoride areas, however no measures of the significance of this association was presented. Needleman (1974) compared the mean age of mothers in the two study areas and found that maternal age was 34.0 in the high fluoride group and 33.2 in the low fluoride group. The author suggested this was enough to account for the observed differences in the incidence of Down’s syndrome found in this study.

Three of the five studies looking at the association between mortality and water fluoridation used standardisation to control for the influence of age, sex and ethnicity (Erickson 1978, Hagan 1954, Rogot 1978). Two of these studies found a negative direction of association; no association was found in the other. None of these studies presented variance data.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome</th>
<th>Reason</th>
<th>Authors Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (1995)</td>
<td>Congenital malformation</td>
<td>No adequate control area - the control area contains &lt;1.5ppm which would be considered a high fluoride area in most studies</td>
<td>There was an increased incidence of spina bifida occulta in children expose to high fluoride (4.5 or 8.5ppm) compared to those expose to low fluoride (&lt;1.5ppm)</td>
</tr>
<tr>
<td>Karthikeyan (1996)</td>
<td>Skeletal fluorosis</td>
<td>Areas selected because they were known to have a high incidence of fluorosis and then water fluoride level investigated. Reasons other than the fluoride content of the water are also investigated for the incidence of fluorosis</td>
<td>Skeletal fluorosis was only present in one of the fluorosis regions, the area which had the highest water fluoride content (3.8-8.0)</td>
</tr>
<tr>
<td>Latham (1967)</td>
<td>Nail mottling and prevalence of goitre</td>
<td>The results are not broken down as much as the water fluoride levels, giving very wide ranges of fluoride levels in some of the areas for which results are presented. All the areas are fluoridated at above 1ppm and some with fluoride levels as high as 45.5ppm.</td>
<td>Author does not specifically relate results to water fluoride content of the area - he comments generally on the results seen in the whole sample studies, as all areas are exposed to comparatively high levels of fluoride. The percentage of people with mottled nails was high in all areas (&gt;26%) as the prevalence of goitre (12-41%). As these results are not specifically related to the water fluoride level and there was no control area it is difficult to link these findings to the water fluoride levels.</td>
</tr>
<tr>
<td>Freni (1994)</td>
<td>Birth rates</td>
<td>The way fluoride exposure is classified is unclear and misleading; the mean fluoride level in the control areas is sometimes higher than the mean fluoride level in the exposed areas.</td>
<td>A negative association was found between high fluoride levels in drinking water and lower birth rates.</td>
</tr>
<tr>
<td>Heasman (1962)</td>
<td>Mortality</td>
<td>The range of water fluoride levels in some of the areas classified as exposed overlaps with the fluoride range in the areas classified as control areas.</td>
<td>The results indicate that the overall mortality was the same in the fluoride and control areas, specific causes of death differences reaching significance at the 5% level. These were conflicting and it was considered very unlikely that fluoride was the cause.</td>
</tr>
<tr>
<td>Morgan (1998)</td>
<td>Dental fluorosis and childhood behaviour problems</td>
<td>Children classified according to Dean’s classification for fluorosis and then fluoride exposure examined. Childhood behaviour problems classified according to dental fluorosis levels not water fluoride levels</td>
<td>the use of supplemental fluoride prior to age 3 was found to be a risk factor for dental fluorosis. No significant association was found between fluoride history variables in aggregate (including water fluoride level) and dental fluorosis. Dental fluorosis was not significantly associated with behaviour problems in the children studied</td>
</tr>
<tr>
<td>Packington (2000)</td>
<td>Fetal, perinatal and infant mortality, congenital malformations and Down’s syndrome</td>
<td>Years of data used not the same. No description of methods, unclear exactly how data presented were calculated. Graphs unclear</td>
<td>Fetal, perinatal and infant mortality, congenital malformations and Down’s syndrome are higher in fluoridated areas of England than in non-fluoridated areas.</td>
</tr>
<tr>
<td>Mitchell (1991)</td>
<td>Sudden Infant Death Syndrome</td>
<td>Data presented graphically. No figures presented in the text. Data could not be read accurately from the graph.</td>
<td>There is no indication of a relationship between fluoridation of the water supply and SIDS in New Zealand.</td>
</tr>
</tbody>
</table>
10.2 Studies that met inclusion criteria but were not included in the main analysis

The eight studies in Table 10.3 were not included in the main analysis of other possible negative effects of water fluoridation for the reasons listed. In three of these studies (Gupta 1995; Freni 1994; Heasman 1962) the control areas included areas that would be considered fluoridated, making interpretation of the results impossible. Data from the other studies were not extracted because of the way the data were presented. Four of these studies conclude that they found a negative relationship with the outcome studied and water fluoridation, two found no association and two did not present clear conclusions.

10.3 Discussion

Interpreting the results of the other possible negative effects is very difficult because of the small number of studies that met inclusion criteria on each specific outcome, the study designs used and the low study quality.

The quality of the research on these topics was generally low, evidence level C (mean of 2.7 out of 8 on validity assessment). Given that all the studies are from lowest the level of evidence with the highest risk of bias, the conclusions should be treated with caution.

A major weakness of these studies generally was the lack of control for any possible confounding factors, many of which were highlighted by the study authors. If the populations being studied differed in respect to other factors that are associated with the outcome under investigation then the outcome may differ between these populations leading to an apparent association with water fluoride level. What is clear is that any further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

Overall, the studies examining other possible negative effects provide insufficient evidence on any particular outcome to reach conclusions.
11. OBJECTIVE 5

Are there differences in the effects of natural and artificial water fluoridation?

In order to investigate whether there are differences in the effects of artificially and naturally fluoridated water on positive (caries) and negative (e.g. cancer) outcomes, each of these outcomes will be considered separately. Unfortunately studies of artificially fluoridated areas rarely report what form of fluoride had been used (e.g. sodium fluoride or silicated fluoride). Consequently, identifying the effects of the various forms of fluoride used in artificial fluoridation schemes separately was not possible.

11.1 Caries studies

Only one study compared a naturally fluoridated area, an artificially fluoridated area and a control area using a before and after study design. This was the Brantford-Sarnia-Stratford study (Brown, 1965) in which Brantford was artificially fluoridated, Stratford was naturally fluoridated and Sarnia was the control area. The proportion of caries-free children and the DMFT was measured at baseline (3 years after fluoridation was introduced in Brantford) and then again seven years later, in children aged 9-11 and 12-14 years. Table 11.1 shows the results of this study.

Table 11.1 Caries experience in naturally, artificially and non-fluoridated areas.

<table>
<thead>
<tr>
<th>Age</th>
<th>Outcome</th>
<th>Brantford (artificial F)</th>
<th>Stratford (natural F)</th>
<th>Sarnia (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
</tr>
<tr>
<td>9-11</td>
<td>% caries-free</td>
<td>5.7</td>
<td>43.8</td>
<td>52.1</td>
</tr>
<tr>
<td>12-14</td>
<td>% caries-free</td>
<td>1.2</td>
<td>18.7</td>
<td>27.2</td>
</tr>
<tr>
<td>9-11</td>
<td>DMFT</td>
<td>4.1</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>12-14</td>
<td>DMFT</td>
<td>7.7</td>
<td>3.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>

At the baseline survey, caries experience, as measured by the proportion of caries-free children and the DMFT score in both age groups, was relatively high in the control area and the area that had recently started to receive fluoridated water. In the survey conducted seven years later, caries experience remained high in the control area and low in the naturally fluoridated area. In the artificially fluoridated area, decay had declined to levels approaching those seen in the naturally fluoridated area. This suggests that naturally and artificially fluoridated water have similar effects on dental decay.

11.2 Possible negative effect studies

11.2.1 Dental fluorosis

A total of 88 studies investigating the association of dental fluorosis and water fluoridation were identified. Of these, 14 did not state whether the water was artificially or naturally fluoridated, 20 compared an area artificially fluoridated (0.6-1.2ppm) with areas of low (<0.3ppm) or very high (4-7ppm) natural fluoride content. The remaining studies only considered naturally fluoridated areas. There were no studies in which an area with water naturally fluoridated to around 1ppm was compared with an area artificially fluoridated to this level. It was therefore not possible to make a direct comparison of the difference in the effect of the naturally fluoridated water compared with artificially fluoridated water.

A term for type of fluoridation (artificial or natural) was included in the regression analysis. This variable did not show an association with fluorosis incidence, suggesting that there is no difference in the effects of artificially and naturally fluoridated water on the incidence of dental fluorosis.

11.2.2 Bone fracture and bone development problems

A total of 29 studies were identified which looked at fracture incidence. Nine compared areas naturally fluoridated at 1ppm with areas of a low natural fluoride level. Eight studies compared areas with different levels of naturally occurring fluoride in the water. Five studies compared areas with mixed (artificial and natural) water fluoride exposure (for example, considering the number of years or proportion of the population exposed to fluoridated water). Seven studies did not state whether the water was artificially or naturally fluoridated. There were no studies in which an area with water...
naturally fluoridated to around 1ppm was compared with an area artificially fluoridated to this level. It was therefore not possible to make a direct comparison of the effects of naturally fluoridated compared with artificially fluoridated water.

11.2.3 Cancer studies

A total of 26 studies looking at the association of cancer incidence with water fluoridation were found. Twelve studies compared areas with artificially fluoridated water with areas with a low natural fluoride content. Three compared areas with different natural water fluoride levels; one compared areas with mixed (both artificially and naturally fluoridated) water fluoridation; and eight studies did not state whether the water was artificially or naturally fluoridated. There were no studies in which an area with natural fluoride levels around 1ppm was compared with an area artificially fluoridated at this level. It was therefore not possible to make a direct comparison of the difference in effects of naturally fluoridated compared with artificially fluoridated water.

Table 11.2 shows the direction of the association of the water fluoride level with osteosarcoma or bone, joint and overall cancer incidence and mortality for each of these studies, and whether the study compares areas with artificial, natural or mixed water supplies.

There were only two studies that considered areas containing only naturally fluoridated water and so it is difficult to draw conclusions from these results. However, the data suggest that there is no statistically significant association between water fluoridation and cancer incidence, irrespective of whether the fluoridated area is artificially or naturally fluoridated.

Table 11.2 Association of cancer incidence and mortality with water fluoride level by method of fluoridation (artificial, natural, not stated)

<table>
<thead>
<tr>
<th>Artificially or Naturally fluoridated</th>
<th>Author (Year)</th>
<th>Cancer</th>
<th>Statistically significant association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial</td>
<td>Chilvers (1983)</td>
<td>All cause</td>
<td>No</td>
</tr>
<tr>
<td>Artificial</td>
<td>Cook-Mozaffari (1981)</td>
<td>All cause</td>
<td>Not stated</td>
</tr>
<tr>
<td>Artificial</td>
<td>Smith (1980)</td>
<td>All cause</td>
<td>Yes (positive effect)</td>
</tr>
<tr>
<td>Artificial</td>
<td>Goodall (1980)</td>
<td>All cause</td>
<td>Not stated</td>
</tr>
<tr>
<td>Artificial</td>
<td>Richards (1979)</td>
<td>All cause</td>
<td>No</td>
</tr>
<tr>
<td>Artificial</td>
<td>Schlesinger (1956)</td>
<td>All cause</td>
<td>Not stated</td>
</tr>
<tr>
<td>Artificial</td>
<td>Raman (1977)</td>
<td>All cause</td>
<td>Not stated</td>
</tr>
<tr>
<td>Artificial</td>
<td>Mahoney (1991)</td>
<td>Bone</td>
<td>Not stated</td>
</tr>
<tr>
<td>Artificial</td>
<td>Hoover (1991)</td>
<td>Bone and joint</td>
<td>No</td>
</tr>
<tr>
<td>Artifical</td>
<td>Hrudey (1990)</td>
<td>Osteosarcoma</td>
<td>No</td>
</tr>
<tr>
<td>Artificial</td>
<td>Mahoney (1991)</td>
<td>Osteosarcoma</td>
<td>No</td>
</tr>
<tr>
<td>Natural</td>
<td>Chilvers (1985)</td>
<td>All cause</td>
<td>No</td>
</tr>
<tr>
<td>Natural</td>
<td>Hoover (1976)</td>
<td>All cause</td>
<td>No</td>
</tr>
<tr>
<td>Natural</td>
<td></td>
<td>Bone</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>Lynch (1985)</td>
<td>All cause</td>
<td>Yes (negative effect) in 2 of 6 analyses</td>
</tr>
<tr>
<td>Other</td>
<td>Kinlen (1975)</td>
<td>Bone</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>Gelberg (1995)</td>
<td>Osteosarcoma</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>McGuire (1991)</td>
<td>Osteosarcoma</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>Moss (1995)</td>
<td>Osteosarcoma</td>
<td>No</td>
</tr>
</tbody>
</table>

11.2.4 Other possible negative effects studies

A total of 31 studies were included in the main analysis assessing the association of other possible adverse effects of water fluoride concentration. Of these, five studies compared areas artificially fluoridated to the 1ppm level with areas with a low natural fluoride level, 11 studies compared areas with different levels of naturally occurring water fluoride levels, and 13 studies did not state whether the areas were artificially or naturally fluoridated. There were two studies in which an area with water naturally fluoridated at around 1ppm was compared with an area artificially fluoridated to this level (Schatz 1976, Rogot 1978). Both studies looked at mortality using a before-after study design, with the baseline survey carried out before water fluoridation was introduced into one of the three study areas. If water fluoride level had a statistically significant effect on mortality, then at the baseline examination mortality would be expected to be higher in the naturally fluoridated area than in the two
other, low fluoride study areas. At the final survey, after fluoridation had been artificially introduced into one of these areas, the mortality rate in the artificially fluoridated area would be expected to show an increase in mortality rate to a level approaching (or surpassing) that seen in the naturally fluoridated area. Neither of these studies showed such an association, and neither study showed a statistically significant difference in mortality rates between the study areas. These data have thus not found any association.

A wide range of outcomes was considered with many outcomes only discussed in one or two studies. There is thus insufficient evidence for any of these outcomes to compare the effects of artificially and naturally fluoridated water.

11.3 Discussion

The assessment of natural versus artificial water fluoridation effects is greatly limited due to the lack of studies making this comparison. Very few studies included both areas with low natural fluoride and areas with high natural or artificial fluoride in their studies. In addressing the question of Objective Five for caries studies there was only one study that could be included. The validity assessment (4.5) of this evidence level B study was slightly below the average (5.0) for the caries studies overall. This study was done in Canada and did not control for potential confounding factors in the analysis. The confidence with which the question can be answered by a single study of moderate validity is low.

The ability to address the question of Objective Five with respect to the effect of natural versus artificial fluoridation on negative effects is also low, as there were no direct comparisons of artificial versus natural water fluoride presented.

As the measure of effect estimates reported in all of the bone fracture studies were similar, no difference in the effect based on artificial or natural fluoridation was expected.

There were not enough studies on cancer incidence and mortality reporting the use of only a natural source of fluoride to adequately compare to those reporting only artificial sources (Table 11.2). There were also no studies using mixed (artificial/natural) water supplies that stratified on this basis. From the data presented, no differences are apparent.

For other potential adverse effects, it was not possible to determine the effects of natural versus artificial sources of water fluoridation. In addition to the overall low quality of studies, there were not enough studies on any particular outcome with subjects exposed to different sources of water fluoride to make adequate comparisons.
12. CONCLUSIONS

The conclusions of this systematic review of water fluoridation are as follows:

12.1 Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

The best available evidence (level B) from studies on the initiation and discontinuation of water fluoridation suggests that fluoridation does reduce caries prevalence, both as measured by the proportion of children who are caries-free and by the mean dmft/DMFT score. The degree to which caries is reduced, however, is not clear from the data available. The range of the mean difference in the proportion (%) of caries-free children is -5.0 to 64%, with a median of 14.6% (interquartile range 5.05, 22.1%). The range of mean change in dmft/DMFT score was from 0.5 to 4.4, median 2.25 teeth (interquartile range 1.28, 3.63 teeth). It is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free (interquartile range of study NNTs 4, 9). The best available evidence on stopping water fluoridation indicates that when fluoridation is discontinued caries prevalence appears to increase in the area that had been fluoridated compared with the control area. Interpreting from this data the degree to which water fluoridation works to reduce caries is more difficult. The studies included for Objective 1 were of moderate quality (level B), and limited quantity.

12.2 Objective 2: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

An effect of water fluoridation was still evident in studies completed after 1974 in spite of the assumed exposure to fluoride from other sources by the populations studied. The meta-regression conducted for Objective 1 confirmed this finding. The studies included for Objective 2 were also of moderate quality (level B), but of limited quantity.

12.3 Objective 3: Does fluoridation result in a reduction of caries across social groups and between geographical locations?

The available evidence on social class effects of water fluoridation in reducing caries appears to suggest a benefit in reducing the differences in severity of tooth decay (as measured by dmft/DMFT) between classes among five and 12 year-old children. No effect on the overall measure of proportion of caries-free children was detected. However, the quality of the evidence is low (level C), and based on a small number of studies. The association between water fluoridation, caries and social class needs further clarification.

12.4 Objective 4: Does fluoridation have negative effects?

The possible negative effects of water fluoridation were examined as broadly as possible. The effects on dental fluorosis are the clearest. There is a dose-response relationship between water fluoride level and the prevalence of fluorosis. Fluorosis appears to occur frequently (predicted 48%, 95% CI 40 to 57) at fluoride levels typically used in artificial fluoridation schemes (1 ppm). The proportion of fluorosis that is aesthetically concerning is lower (predicted 12.5%, 95% CI 7.0 to 21.5). Although 88 studies of fluorosis were included, they were of low quality (level C). The best available evidence on the association of water fluoridation and bone fractures (27 of 29 studies evidence level C) show no association. Similarly, the best available evidence on the association of water fluoridation and cancers (21 of 26 studies evidence level C) show no association. The miscellaneous other adverse effects studied did not provide enough good quality evidence on any particular outcome to reach conclusions. The outcomes related to infant mortality, congenital defects and IQ indicate a need for further high quality research, using appropriate analytical methods to control for confounding factors. While fluorosis can occur within a few years of exposure during tooth development, other potential adverse effects may require long-term exposure to occur. It is possible that this long-term exposure has not been captured by these studies.
12.5 Objective 5: Are there differential effects of natural and artificial fluoridation?

The evidence on natural versus artificial fluoride sources was extremely limited, and direct comparisons were not possible for most outcomes. While no major differences were apparent in this review, the evidence is not adequate to reach a conclusion regarding this objective.

12.6 Limitations of this systematic review

In conducting a large systematic review that extends back to the late 1930’s, limitations are inevitable. The primary limitation of the review is the quality of the research included.

The first limitations revolve around the search strategies. More non-English language databases (particularly Russian and Chinese) could have been searched. The impact of failing to search such databases is unknown and the logistic and financial impact of trying to do so would be significant. Some reports were difficult to obtain. However, out of over 730 articles, only 14 were not retrieved. Attempts were made to contact authors to assist in locating further reports, but due to the age of the research were not successful. Additional difficulties were encountered in obtaining some theses and dissertations. Given the comprehensive nature of the search, the completeness of retrieval, and the openness of the review process to the public, the review team feels that it is unlikely that a key study of sufficient size and quality to change any of the findings was missed.

Even comprehensive searches such as that used here may result in a biased collection of studies. Since studies showing a statistically significant result are more likely to be published, the set of published studies located may represent a biased sample and over-estimate an effect (positive or negative).

The validity assessment of the included studies (Appendix D) used a checklist scoring system. This approach can be criticised for lack of sensitivity, in that studies are assessed for having done the items on the list, but not necessarily how well they were conducted. For example, a study could receive points for controlling for confounding factors, but the analysis may not have been performed correctly.

The lack of variance data in some studies, particularly for Objectives 1 and 2, limited the amount of data that could be included in the analyses. Insufficient data prevented statistical pooling of data on social class effects, cancer, other adverse effects, and natural versus artificial fluoride effects. Generally, low to moderate study qualities limit the strength of the possible inferences that can be made.

Some of the studies included in the meta-regression analyses contribute more than one observation to the meta-analysis. It has been assumed in the meta-regression analyses that these observations are independent, and hence each estimate has been treated as though it came from a separate study. For example for studies that report results stratified by age but present no summary measure, results for all strata are included separately in the analysis. However, this approach may introduce bias in the results. Any confounding factors not controlled for, or bias in the study design is likely to be similar for all estimates coming from the same study. Including these estimates as separate estimates in the regression analyses could have the effect of compounding these sources of bias. Study level variables, such as study length and validity score, will also be the same for all the estimates that come from a single study. The direction or degree of any effect of this potential bias is unknown.

12.7 Other factors to be considered

The scope of this review is not broad enough to answer independently the question ‘should fluoridation be undertaken on a broad scale in the UK’? Important considerations outside the bounds of this review include the cost-effectiveness of a fluoridation program, total fluoride exposure from environmental and non-environmental sources other than water, environmental and ecological effects of artificial fluoridation and the ethical and legal debates. This review did not include animal or laboratory studies because studies on humans were available and would give more reliable estimates of any potential benefits and harms.
12.7.1 Economic analysis

If a benefit of water fluoridation on caries occurrence was demonstrated, the cost-effectiveness of such an intervention relative to other strategies would need to be carefully considered. The search strategies used in this review did not specifically identify research related to the cost-effectiveness of water fluoridation. A search of the NHS Economic Evaluation Database did not identify any recent studies meeting the criteria for a full economic evaluation.

This review is presenting new information on the effectiveness of water fluoridation in preventing caries and the effects on fluorosis, which previous economic analyses would not have had.

12.7.2 Total fluoride exposure

There is some suggestion that total fluoride exposure has increased over recent years, particularly in industrialised nations. Exposure to fluoride from sources other than water may alter the amount required in water for optimum caries reduction and is thus a potential confounding factor in studies of the association between water fluoridation and negative effects. Because sources of fluoride exposure vary, this may be a difficult issue to examine, in that exposure would need to be measured at the person level, rather than at the population level. However, if two study areas are comparable, in all respects, the fluoride exposure from non-water sources (e.g. tea) should also be similar. There are studies that have measured total fluoride exposure in people exposed to fluoridated and non-fluoridated water, but these did not meet inclusion criteria for this review (Guha-Chowdhury, 1996, Mansfield, 1999). Because of potential toxicity of very high doses of fluoride, it would seem sensible that any future studies should attempt to measure total fluoride exposure in areas being researched.

12.8 Information to guide practice

The available evidence shows that water fluoridation reduces the prevalence of caries. The median difference between fluoridated and non-fluoridated areas in the proportion of children who are caries-free is 14.6%, while the reduction in the number of teeth affected (dmft/DMFT score) is 2.3. The available evidence shows that fluorosis occurs in approximately 48% of the population at water fluoridation levels of 1.0ppm. The proportion who have teeth that are affected enough to cause aesthetic concern is approximately 12.5%. The quality of these data on benefit and harm is in general only low to moderate, and should be interpreted with caution, especially considering the significant heterogeneity between studies. The benefit and harm data need to be considered in conjunction when making decisions about water fluoridation.

12.9 Implications for research

Although there has been considerable research in this area, the quality is generally low. The research needs that have been identified through this systematic review are described below.

12.9.1 Caries studies

The two most important factors missing from the current set of studies are adjusting for confounding factors using standard analytic techniques, and reporting variance data. In addition to the potential confounding factors noted in section 4.2.2, frequency of sugar consumption, measurement of total exposure to all sources of fluoride, the number of erupted teeth per child, and the level of spending on dental health in intervention and control areas should be included. Blinding of observers should be attempted and at least standardisation of the assessment would be essential to reduce the potential impact of observer bias. Studies should also consider changes in social class structure over time. Only one included study addressed the positive effects of fluoridation in the adult population. Assessment of the long-term benefits of water fluoridation is needed.

It would be logical to include an assessment of adverse effects alongside any future study of caries. While fluorosis may be evident in young populations within a few years of starting fluoridation, other potential adverse effects may take longer to occur, or may occur largely in an adult population.

Most of the evidence on social class effects of fluoridation was from cross-sectional studies of low quality. If further studies are considered, social class effects could be incorporated into a study of fluoridation efficacy. More research into the most appropriate tool to measure social class in relation to dental health is also needed.
12.9.2 Adverse effects studies

The results of this review suggest that a dose-response relationship exists between water fluoride level and the prevalence of fluorosis. Future studies should address the impact of using lower levels of water fluoride content, such as 0.8ppm in a formal way in conjunction with an efficacy study. The potential confounding factors and causes of between study heterogeneity identified in this review should be controlled for in the analysis.

With bone fracture and cancer studies, the evidence is very balanced around the 'no effect' mark. If any further research is considered, controlling for confounding factors and ensuring adequate blinding should be a priority.

The other possible adverse effect studies suffered greatly by not sufficiently controlling for important confounding factors, many of which were discussed by authors in the study reports, but not controlled for. Very few of the possible adverse effects studied appeared to show a possible effect. High quality research that takes confounding factors into account is needed.

12.9.3 Economic evaluations

When evaluating the cost-effectiveness of an intervention such as water fluoridation, there are key factors to be considered. The costs of the intervention are weighed against the benefits. A full economic evaluation of water fluoridation should include a complete accounting of the potential costs of the intervention (cost of fluoridating, administration costs, and quality assurance costs) and the benefits. Examples of the benefits that should be included are the reduction in caries that is assumed, any changes in the number of dental visits, procedures, and long-term effects such as changes in the need for dentures. The quality of life (QOL) of those who receive the intervention should be measured, in comparison to those not receiving the intervention (such as the effect of not losing teeth to caries, the effect of having fluorosed teeth, anxiety associated with dental visits, and dental pain). Indirect costs of travel time and time off work for parents to take children to the dentists could also be included. Such an economic evaluation could be done along side an intervention study measuring actual resource use and costs, or as a modelling exercise using the most accurate efficacy data (e.g. from this systematic review). Differences in dental resource use among social classes should also be investigated.

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We note that NFIS continues to quote the “Paekakariki Study” by Dr Neal Stephen, even though this was exposed as scientific nonsense following an Official Information request from KCDC councillor Peter Daniel. This “study” had so few children in it that it was statistically and scientifically worthless.

Hastings presentation by Whyman and Beasley

International evidence

  - 15% or more children and adolescents with one or more teeth affected
  - Between 0.6 and 2.25 more teeth per person affected
  - Effect greater for some children and less for others
The authors commented: We are concerned about the continuing misinterpretations of the evidence and think it is important that decision makers are aware of what the review really found. We were unable to discover any reliable good-quality evidence in the fluoridation literature world-wide.

The York review rejected over 90% of studies claiming a benefit from fluoridation to be so poor that it rejected them outright.

The figures quoted were NOT a proven benefit. They were just the figures of the median study of 30 studies, which ranged from 5% MORE tooth decay in fluoridated areas to 64% less – the bars on the chart.

The authors commented: The quality … is in general only low to moderate, and should be interpreted with caution, especially considering the significant heterogeneity between studies.

No study used an analysis that would control for the frequency of sugar consumption or the number of erupted teeth per child.

What evidence we found suggested that water fluoridation was likely to have a beneficial effect, but that the range could be anywhere from a substantial benefit to a slight disbenefit to children's teeth.

The evidence about reducing inequalities in dental health was of poor quality, contradictory and unreliable.
Adult dental decay and tooth loss

Water fluoridation responsible for preventing 27% of adult tooth decay
Griffin et al Journal of Dental Research 2007;86:410-415

This is not correct – Griffin did not say this.

Griffin is not research: it is a review of research. But only research published in English.

Griffin’s opening statement is:

To date, no systematic reviews have found fluoride to be effective in preventing dental caries in adults.

Then at pages 413 and 414 it states:

One limitation of this review is the quality and the quantity of studies on fluoride effectiveness among adults.

There is a clear need for further well designed studies on the effectiveness of fluoride among adults.

In particular, Griffin took results of studies that found no statistically valid benefit and used them as if there was a real benefit.
Regarding the 27% figure, Griffin is misquoted. Griffin does not say fluoridation reduces adult tooth decay by 27%.

Griffin said there were three things that reduced adult tooth decay:

- Professionally applied fluoride (e.g. gels and lacquer)
- Self applied fluoride (e.g. toothpaste)
- Fluoridated water (based on invalid studies).

The total reduction was 0.51 DMFS. No percentage is stated.

Griffin claimed that water fluoridation was responsible for 27% of that 0.51 DMFS reduction. If the 0.51 DMFS represented a 50% reduction, water fluoridation reduced decay by 13.5%. If it was a 30% reduction, water fluoridation reduced decay by 8.1%.

But a reality check tells us Griffin’s finding is not credible.

The reduction of 0.51 DMFS was claimed to be annual.

If we assume this is a 50% reduction, this means that in fluoridated areas such as Wellington a person with no fillings at age 18 would have 10 by age 38 and 20 by age 58. In an unfluoridated area such as Christchurch, a person with no fillings at age 18 would have 20 by age 38 and 40 by age 58.

The benefits of water fluoridation are greatest in communities with high proportions of children, Maori, and/or people of low socio-economic status.


However the figures quoted actually show that any “benefit” is only temporary, disappearing to zero benefit by age 14. And the temporary apparent benefit was only 0.2 to 0.3 DMFT.
This is consistent with Armfield and Spencer's 2004 research across the board: there was no permanent benefit from age 12, with only a temporary apparent benefit before that.

This is quoted out of context. The Privy Council actually held:

**a)** That “pure water” meant wholesome (in the normal English sense), not chemically pure, water.

**b)** That the power to provide “pure water” did not prevent the addition of medication such as fluoride provided the water remained “wholesome”

3. **a)** The Privy Council ruled that fluoridation was medication:

   Their Lordships are of the opinion that … as a matter of common sense there is but little difference for the relative purpose between the adjectives "pure" and...
"wholesome". Their Lordships think it an unnecessarily restrictive construction to hold (as did McGregor J.) that, because the supply of water was already pure there is no power to add to it constituents merely to provide medicated pure water, i.e. water to which an addition is made solely for the health of the consumers.

The Privy Council confirmed its acceptance of the findings of the lower courts on the point of fact, that fluoridating water did not make the water less "wholesome", which would be prohibited:

The water of Lower Hutt is no doubt pure in its natural state ... The addition of fluoride adds no impurity and the water remains not only pure water but it becomes greatly improved and still natural water containing no foreign elements.

b) The passage does not preclude fluoridation from being medication, and the Privy Council declared fluoridation to be medication as above (contrary to the claims of the Ministry of Health who quote the passage as proof that fluoridation is not medication.)

c) This passage does not preclude any court, or any territorial authority, from holding an opposite view based on more recent scientific research.

4. The Local Government Act 2002 does not provide for the supply of “pure” water, but of “drinking water”. Accordingly, the Privy Council ruling is “distinguished”, and does not apply to the LGA 2002

• Human Rights Commission 1980

"In all circumstances therefore, it is considered that the question of fluoridation of water supplies by public authorities does not constitute a denial of human rights."

The HRC had neither the jurisdiction nor the expertise to address anything other than matters of discrimination. The NZ Bill of Rights Act did not come into force until 10 years later, in 1990.

The report quotes the NZ Medical Association’s view that even if fluoridation is forced medication it is permissible because compulsory treatment for VD, immunisation of overseas travelers, and treatment of mental patients are acceptable forced medical treatments. At no point does the Commission recognize the vast difference between
these situations posing a risk to the public at large and tooth decay which poses none, as the US case law does.

The report was written by an office junior. It contains no original or substantial analysis. The Commission sought the views of fluoridation promoters only: the Health Department, NZ Medical Association, and NZ Dental Association. It also reviewed both the NZ Commission of Inquiry’s analysis of this issue, and the Tasmanian 1968 Commission of Inquiry. It describes the New Zealand Commission as considering this issue “at length”, which is incorrect. It also refers to the 1969 recommendation of the World Health Organisation that fluoridation be implemented as a health measure, without reference to human rights implications. It notably does not refer to any analysis by the governments of Europe who rejected fluoridation on human rights grounds amongst others. Neither does it refer to the Jacobsen case.

In short it simply adopts the prevailing political view that fluoridation does not constitute a breach of human rights because people can avoid it even if at considerable cost and inconvenience.

The Commission equates the argument about mass medication to the “false analogy of forced feeding that occures (sic) in respect to people who have gone on hunger strike.” And concludes there is no real similarity as no attempt is made to force people to drink fluoridated water in “a direct physical way.” Such a superficial argument must undermine the credibility of the Commission’s decision on this issue.

Further, we now have Bill of Rights case law such as Noort v Ministry of Transport. The accepted jurisprudence is that citizens be given “full measure” of a right, in this case freedom from compulsory medical treatment, as opposed to a “niggardly” approach (See also Fisher, 1980). He HRC’s niggardly approach is in direct conflict with current case law, and must be rejected as unsound under today’s jurisprudence.
How many of you think that Cressey is saying that halving the fluoride content of formula powder will fix the problem?

He is not. He is confirming past development in formula production. He goes on to say on the same page (Page 5):

"The fluoride content of infant formulae available in New Zealand appears to be at the lower end of the range observed internationally."

"[I]n regions with fluoridated water supplies, the fluoride intake of fully formula-fed infants will be largely due to fluoride from water used for reconstitution, rather than fluoride from the infant formula product."

"Approximate halving of the fluoride content of infant formula on the NZ market should be viewed as a significant development"
• No significant difference in the prevalence of fluorosis between people living in fluoridated and non-fluoridated areas
  
  – 15% had very mild or mild fluorosis
  – 2% moderate fluorosis
  – 0% severe fluorosis

Source: 2009 New Zealand Oral Health Survey

This is deliberate deception, and contradicts the actual NZ research.

Also, the severe figure quoted is 0.0 to 0.8%, not 0%. This contradicts claims by proponents that there is only mild or very mild dental fluorosis in NZ, and no moderate or severe.

The best studies on dental fluorosis are the 2005 Southland study and 2008 Auckland study. Both found a doubling of dental fluorosis – from 15-16% in unfluoridated communities to 30-32% in fluoridated communities.

The Auckland study found no difference in the number or severity of tooth decay. The Southland study found no difference in DMFT or percent caries-free figures. It then claimed a 50% (0.5 dmfs) benefit based on an undisclosed multivariate analysis modeling.

The Oral Health Survey document was not based on research where fluoridation was concerned. At P167 the 2010 publication states:

“It is important to note that it was not one of the objectives of the 2009 NZOHS to compare the oral health status of people by fluoridation status, and therefore the survey cannot be considered a fluoridation study as such. The following results are for a snapshot in time, and constitute an ecological analysis based on current place of residence. As such, they do not take into consideration lifetime exposure to fluoridated and non-fluoridated water supplies. Individuals who currently live in fluoridated areas may have spent time in non-fluoridated areas, and the reverse is also true. Furthermore, there may be other confounding factors that have not been taken into account in this analysis, such as the usual reason for visiting a dental professional, and other sources of fluoride such as fluoride toothpaste.”
Ecological analysis is unsound. There is also no control for socio-economic status – the primary determinant of oral and general health status. Nor is there control for the large number of unnecessary fillings placed in people born before 1972.

Table 92: Prevalence of dental fluorosis, among dentate adults and children aged 9–30 years, by level of fluorosis (unadjusted prevalence)

<table>
<thead>
<tr>
<th>Level of fluorosis</th>
<th>Prevalence (95% CI) among 8–30-year-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>None (level 0)</td>
<td>55.5 (49.0–62.0)</td>
</tr>
<tr>
<td>Questionable (level 1)</td>
<td>27.2 (22.2–32.2)</td>
</tr>
<tr>
<td>Very mild (level 2)</td>
<td>10.2 (6.6–15.0)</td>
</tr>
<tr>
<td>Mild (level 3)</td>
<td>5.1 (2.8–8.1)</td>
</tr>
<tr>
<td>Moderate (level 4)</td>
<td>2.0 (1.7–4.4)</td>
</tr>
<tr>
<td>Severe (level 5)</td>
<td>0.0 (0.0–0.8)</td>
</tr>
</tbody>
</table>

Source: 2009 New Zealand Oral Health Survey

How much does it take (doses required)?

- The primacy of dose as a determinant of risk
- “It is the dose that differentiates a poison from a remedy” - Paracelsus
- Innumerable examples in Toxicology – albeit with fluoride the remedial and toxic doses are less widely separated than in the average case

This is the problem – you cannot control the dose with fluoridation. You cannot even control the dose obtained from drinking water, yet alone the total dose from all sources, since fluoridated water gets into food and commercial drinks, but is not stated on the packaging.

There is no remedial dose of fluoride – it does not work by being swallowed.

This is an admission that small doses of fluoride are toxic. In fact the toxic dose is less than that experienced in fluoridated communities.

At levels of even 0.5 ppm, fluoride can accumulate in bones to the level of Stage 1 skeletal fluorosis, which has the same symptoms as arthritis.

Several studies have shown that other adverse health effects are linked with dental fluorosis – the first outward sign of fluoride poisoning in children (NRC Review 2006)

- De-ionised water? (no Ca²⁺ ions?) - could increase toxicity of F
This acknowledges what opponents have long claimed – that silicofluorides pose a greater health risk than calcium fluoride due to the lack of calcium to balance the fluoride.

The discussion of techniques etc is equally applicable to studies claiming a benefit from fluoridation. In fact these stack up worse against these criteria than studies showing adverse health effects. Yet promoters are more than happy to accept poor quality studies in support of fluoridation while rejecting better quality studies opposing fluoridation. The ESR 2000 report, for example, cited exactly the same methodological flaws in two studies, yet accepted the pro-fluoridation one and rejected the anti-fluoridation one. This is typical of the double standard applied by fluoridation promoters.

<table>
<thead>
<tr>
<th>Population subgroup</th>
<th>Adequate intake (mg/day)</th>
<th>Upper level (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-6 months</td>
<td>0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Infants 7-12 months</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>1-3 years</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>4-8 years</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>9-13 years</td>
<td>2.0</td>
<td>10.0</td>
</tr>
<tr>
<td>14-18 years</td>
<td>3.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 15+ years (including pregnant/lactating women)</td>
<td>4.0</td>
<td>3.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>


There is no scientific basis for these figures. They have been derived solely for the political purpose of continuing fluoridation. The adult upper limit used to be 3 mg/day, but once it was discovered this intake level had become common, it was reclassified as “adequate” and the upper limit increased to 10 mg/day.

First, “adequate dose” means there is no scientifically determined minimum daily requirement, and the “adequate dose” is simply what is commonly consumed without apparent adverse effects. But since no one is looking for adverse effects, this is actually meaningless. The term also gives the false impression that there is a need for fluoride. If there were, there would be a minimum daily requirement (RDI). But there is none.

Also, the upper “safe” limits are scientifically disproved. At 10 mg/day adults will end up with advanced skeletal fluorosis. Even at 1-2 mg/day, Stage I skeletal fluorosis occurs, indistinguishable from arthritis. The 10 mg/day was based on one individual in the USA who drank water from a well with high fluoride concentration. But it also had very high magnesium levels, which protect against fluoride poisoning as does calcium. No one else could drink the water it tasted that bad.

Regarding infants under 6 months, there have been no studies on safety. The blood-brain barrier is not fully formed until 6 months, so infants should be protected for exposure to fluoride, as is the case with breast milk.
The most reliable opinion on this issue is the review conducted by the highest scientific body in the USA – the National Research Council Review published in 2006.

“Osteosarcoma presents the greatest a priori plausibility as a potential cancer target site because of fluoride’s deposition in bone, the NTP animal study findings of borderline increased osteosarcomas in male rats, and the known mitogenic effect of fluoride on bone cells in culture. Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in nondividing states.”


Regarding the above false claims, the National Toxicology Programme states there is a “biologically plausible” link between fluoride exposure and osteosarcoma.

The biological plausibility centers around three facts:

1) Bone is the principal site of fluoride accumulation, particularly during the growth spurts of childhood;
2) Fluoride is a mutagen when present at sufficient concentrations (and mutagens are typically carcinogens), and
3) Fluoride can artificially stimulate the proliferation of bone cells (osteoblasts), that is, it is a mitogen.
As things stand, the weight of evidence shows it is likely that fluoride exposure in the age range 6-8 increases the risk of teenage osteosarcoma in males by 500% or more. In NZ this equates to about two deaths per year due to fluoridation.

Regarding the claims made in the presentation:

**NHMRC.**
This review classed Bassin's study methodology as “fair to good”. This is better than the York Review’s classification of any study claiming fluoridation reduces tooth decay. NHMRC relied solely on a letter to the editor, promising the study mentioned in the presentation (Douglass and Joshipura). It is unheard of for a letter to the editor to be accepted as overriding bona fide research.

In fact the study was published in 2011

In fact his study in much smaller than Bassin’s. Even Douglass admitted the study was so small it could provide no reliable conclusions.

It examined only bone fluoride levels, which measure total lifetime exposure. As Bassin showed, this is irrelevant to osteosarcoma risk. So it did not even address Bassin’s core finding of age-related risk, let alone refute it.

It also has very poor case control, unlike Bassin’s which had excellent case control. Douglass’ control group averaged 41 years old – against the osteosarcoma cases which were in their teens. There was also a significant gender imbalance, yet the effect is specific to males only.

**SCHER**
This review was a whitewash from the outset. The reports have been consistently self contradictory. The final report claims no studies were cited on one particular issue when in fact 140 studies were presented. SCHER refuses to explain why it falsified its report on this point.

In fact there are a number of animal studies showing a link between fluoride and osteosarcoma. However the results were systematically downgraded so as to claim there was no link.
Effectiveness of Fluoride in Preventing Caries in Adults

INTRODUCTION

In systematic reviews on the effectiveness of fluoride in preventing/arresting caries, most of the studies included have been conducted among children (CDC, 2001; National Institutes of Health Consensus Development Conference Statement, 2001). For example, the National Institutes of Health Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life noted that evidence on the effectiveness of fluoride in preventing dental caries was limited to studies involving populations of children between six and 15 yrs of age.

The reviews included in the consensus conference generally emphasized the professional application of fluorides (Treasure, 2001), and not self-applied fluoride or water fluoridation. Moreover, the Centers for Disease Control and Prevention's (CDC) 2001 Recommendations for Using Fluoride to Prevent and Control Dental Caries in the U.S. found that, "Few studies evaluating the effectiveness of fluoride toothpaste, gel, rinse, and varnish among adult populations are available", and called for further research on the effectiveness of different fluoride modalities on dental caries, including adults over 50 yrs old (CDC, 2001).

Documenting the effectiveness of fluoride in preventing/managing dental caries among adults is important. Although literature reviews suggest that the incidence of caries among adults is as high as that in children—about 1 new carious coronal tooth surface per year (Garcia, 1989; Griffin et al., 2005)—with the exception of water fluoridation, virtually all primary preventive programs target children and youth (Association of State and Territorial Dental Directors, 2002). One possible reason for the lack of preventive programs for adults may be the lack of evidence on their effectiveness for this population. To compete successfully for resources to support primary prevention, programs must not only establish the importance of the problem, but also provide evidence that interventions are effective (Gooch et al., 2006).

For this present study, we analyzed the topical effectiveness of fluoride (self- and professionally applied and in drinking water) in preventing/reversing caries in all adults (aged 20+ yrs) and in older adults (aged 40+ yrs). Because several clinical trials on the effectiveness of fluoride were conducted in the 1950s and 1960s, we expanded our search to include articles published before 1980, the earliest year in the National Institutes of Health search for systematic reviews (Rozier, 2001). We specifically addressed the following questions: (1) Is fluoride effective in preventing coronal caries in all adults and in older adults (≥40 yrs) and in preventing root caries in the older group? and (2) How effective are the different fluoride delivery modes in preventing caries?

METHODS

Search Strategy

We searched three electronic databases to locate primary studies and systematic reviews relating to the topical effectiveness of fluoride (i.e., fluoridated water or fluoride-containing toothpaste, gel, varnish, or rinse) in preventing or arresting caries among adults:

ABSTRACT

To date, no systematic reviews have found fluoride to be effective in preventing dental caries in adults. The objective of this meta-analysis was to examine the effectiveness of self- and professionally applied fluoride and water fluoridation among adults. We used a random-effects model to estimate the effect size of fluoride (absolute difference in annual caries increment or relative risk ratio) for all adults aged 20+ years and for adults aged 40+ years. Twenty studies were included in the final body of evidence. Among studies published after/during 1980, any fluoride (self- and professionally applied or water fluoridation) annually averted 0.29 (95%CI: 0.16-0.42) carious coronal and 0.22 (95%CI: 0.08-0.37) carious root surfaces. The prevented fraction for water fluoridation was 27% (95%CI: 19%-34%). These findings suggest that fluoride prevents caries among adults of all ages.

KEY WORDS: caries, fluoride, adults, meta-analysis.
(1) MEDLINE from 1966 to week 42 of 2004 (Appendix Table 1) identified 1044 records;
(2) EMBASE from 1988 to week 43 of 2004 (Appendix Table 2) identified 56 records; and
(3) in the Cochrane Control Register of Controlled Trials (CENTRAL), we used MEDLINE search strategy to identify 148 records.
Two reviewers (VH and SG) independently reviewed the abstract and title of each record for relevant articles; records deemed relevant by at least one reviewer were examined. In addition, the references of each retrieved article were searched for relevant articles. In total, 489 articles were examined and screened with a form developed for this review (Appendix Table 3). We also contacted the American Dental Association, the Food and Drug Administration, and manufacturers of topical fluoride products for unpublished clinical trials (Appendix Table 4), but these inquiries did not yield additional studies.

**Study Selection and Validity Assessment**

A study was eligible for abstraction if it was published in English, lasted 1 yr or longer, and examined the association between fluoride and caries in intact human teeth in study populations that included adults. In all, we reviewed 50 studies (Appendix Fig. 1). Studies were excluded from the final body of evidence if the mean age of the study population was less than 20 yrs, they did not have a concurrent control group, or there was insufficient information to both extrapolate the benefits of fluoride to all 28 teeth and to calculate a standard error (Appendix Tables 5, 6).

We used an algorithm designed by the Guide to Community Preventive Services to determine the type of study design (Zaza et al., 2000). To examine the effectiveness of self- or clinically applied fluoride, we included only longitudinal studies with random assignment of participants or of split-mouth design. For studies examining the effectiveness of water fluoridation, we included cross-sectional studies if their participants lived most of their lives (hereafter referred to as "lifetime residency") in fluoridated/non-fluoridated communities, or they estimated the effect of exposure to water fluoridation controlling for potential confounding factors. Because water fluoridation is a community intervention, it is difficult to assign participants randomly to a treatment or control group, and thus other systematic reviews of the effectiveness of water fluoridation have not excluded non-randomized studies (McDonagh et al., 2000). Other measures of validity (drop-out rate and examiner/participant blinding) were also examined and reported for included studies, but were not used to exclude studies.

**Data Abstraction**

All four authors pilot-tested an abstraction form developed for this project (Appendix Table 7). To calibrate the reviewers, all four reviewers abstracted the same five articles and then met to discuss and compare their completed abstraction forms. After a consensus had been reached on how the form should be completed, each article was randomly assigned to two reviewers. All four reviewers independently abstracted their assigned articles and then compared abstraction forms with the other reviewer to whom the article had been assigned; finally, the two reviewers completed a consensus abstraction form.

**Outcome Measures**

The primary outcome of interest was coronal caries increment, as measured by the number of teeth/surfaces becoming decayed or filled (DMFT/S) or decayed, filled, or missing (DMFT/S). We examined this outcome in all adults (20+ yrs) and in adults (40+ yrs). We also estimated the root caries increment for adults, aged 40+ yrs. We chose 40 yrs as the cut-point age to balance age with the need to have a sufficient number of studies.

The reader should note that, for the cross-sectional studies with lifetime exposure to fluoridated/non-fluoridated water, DMFT/S prevalence measures lifetime caries increment or, if divided by the number of teeth/surfaces (assumed to be 28 teeth/128 surfaces), estimates the lifetime attack rate (% of teeth or surfaces attacked by caries).

**Adjustment of Outcome Measures**

When adjusting data, we used conservative methods that would bias the results against a statistical finding of a benefit of fluoride. For studies that reported the absolute difference in caries increment for the same population for different time intervals (e.g., 12 and 30 mos), we used the results for the follow-up examination that was closest to, but at least 1 yr after, the first examination, so that the method used to annualize the variance would have minimal influence. For studies whose selected follow-up period exceeded 1 yr, we annualized the outcome measure by assuming that caries increment was constant, and therefore independent of the duration of the time since the first examination. Thus, we annualized the reported caries increment by dividing it by the number of yrs in the reported interval, and estimated the annual standard error by dividing the reported standard error for the interval by the square root of the number of years in the interval. If the caries increment were higher in the first year and the caries increment in the control group were higher than in the treatment group (as expected), the above method would underestimate the absolute difference in caries increment attributable to fluoride exposure.

**Quantitative Data Synthesis**

To examine if any fluoride is effective, we used Fisher's inverse chi-square method (Hedges and Olkin, 1985) to calculate whether combined p-values were statistically significant. This test statistic was calculated for studies examining the effectiveness of any mode of fluoride delivered to all and older adults. We also applied Fisher's test to the water fluoridation studies, because they also had different outcome measures and used different statistical methods.

To measure the size of the effect of water fluoridation, we calculated the relative risk ratio for each of the cross-sectional studies that excluded participants without continuous residency, where

\[
\text{Relative risk} = \frac{\% \text{ teeth or surfaces that are DMFT}_{\text{Fluoridation}}}{\% \text{ teeth or surfaces that are DMFT}_{\text{Control}}}
\]

We used the relative risk ratio because it is more invariant to differences in unit of measurement (teeth vs. surfaces), baseline caries risk status, and age (length of exposure), which were all possible confounding factors. To calculate the standard error for the relative risk ratio, we assumed perfect correlation among teeth (the most conservative assumption), and thus the effective sample size became the number of participants; we used this value in calculating the pooled standard error.

For the remaining studies, we used the absolute difference in annual caries increment between the control and the treatment groups to measure the effect size.

For those studies where the standard error had to be extracted from reported p-values, or it was necessary to pool standard errors to make comparisons similar across studies, we used standard statistical techniques, which are described in the Notes Section of
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design; Number of Subjects; Duration; Drop-out Rate</th>
<th>Location; Mean Age in Yrs (Range)</th>
<th>Mode of Fluoride Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt et al., 1986;</td>
<td>Cross-sectional; 315; NA; NA</td>
<td>New Mexico; 41.6 (27-65)</td>
<td>Community water system (3.5 ppm&lt;sup&gt;a&lt;/sup&gt; vs. 0.7 ppm)</td>
</tr>
<tr>
<td>Eldlund et al., 1987</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DePaula, 1993</td>
<td>Randomized controlled trial; 71; 1 yr; 14%</td>
<td>Northeastern US; 71 [NR]</td>
<td>Gel (1.2%) professionally applied for 2 min every 4 mos, and daily self-application of neutral sodium fluoride gel (0.5%)</td>
</tr>
<tr>
<td>Englander and Wallace,</td>
<td>Cross-sectional; 1831; NA; NA</td>
<td>Illinois; 33 (18-59)</td>
<td>Community water system (1.2 ppm vs. 0.1 ppm)</td>
</tr>
<tr>
<td>1962</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fure et al., 1998</td>
<td>Randomized controlled trial; 81; 2 yrs; 6.8%</td>
<td>Sweden; 71.5 [NR]</td>
<td>Rinse (0.05%) twice daily</td>
</tr>
</tbody>
</table>

<sup>a</sup> Not applicable.  
<sup>b</sup> Parts per million.  
<sup>c</sup> Not reported.

- Results stratified by good (≥ 3 times daily) or bad brushers (≤ 2 times daily), but numbers in each group not reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design; Number of Subjects; Duration; Drop-out Rate</th>
<th>Location; Mean Age in Yrs (Range)</th>
<th>Mode of Fluoride Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grembowski et al., 1992</td>
<td>Cross-sectional; 595; NA; NA</td>
<td>Washington; 30.6 (20-34)</td>
<td>Community water system</td>
</tr>
<tr>
<td>Hunt et al., 1989</td>
<td>Prospective cohort (random sample); 275; 1 yr; 13%</td>
<td>Iowa; 75 (NR)</td>
<td>Community water system (0.7 to 1.5 ppm vs. &lt; 0.5 ppm)</td>
</tr>
<tr>
<td>Jensen and Kohaut, 1988</td>
<td>Randomized controlled trial; 810; 1 yr; 11%</td>
<td>Iowa; 68 (54-93)</td>
<td>Dentifrice (1.1%) used twice daily</td>
</tr>
<tr>
<td>Lu et al., 1980</td>
<td>Randomized controlled trial; 1105; 1 yr; 17%</td>
<td>Oregon; 34 (18-78)</td>
<td>Dentifrice (etanous fluoride-calcium pyrophosphate, pH = 4.5; fluoride content NR)</td>
</tr>
<tr>
<td>Morgan et al., 1992</td>
<td>Cross-sectional; 104; NA; NA</td>
<td>Australia; NR (20-24)</td>
<td>Community water system (fluoride content NR)</td>
</tr>
<tr>
<td>Muhler et al., 1956</td>
<td>Randomized controlled trial; 322; 1 yr; 10%</td>
<td>Indiana; NR (17-36)</td>
<td>Dentifrice (4 mg stannous fluoride; frequency not reported)</td>
</tr>
<tr>
<td>Muhler, 1958</td>
<td>Randomized controlled trial; 435; 1 yr; NR</td>
<td>Indiana; NR (17-38)</td>
<td>Aqueous solution professionally applied (10%), single application</td>
</tr>
</tbody>
</table>

- Age was assumed to be greater than 20 yrs because participants were all dental students.

We estimated summary measures for the various modes of fluoride by age group if there were five or more studies for that mode. We used a random-effects model, which assumes that each study was randomly selected from a hypothetical population of studies (DerSimonian and Laird method, referenced in Normand, 1999). Because we included many studies published before 1980, we also estimated summary measures for studies conducted during or after 1980. We tested for homogeneity of effect size using a chi-square test (Q<sub>χ</sub>) (Normand, 1999). Because we had a small number of studies in many cases, we estimated the quantity I² (Higgins and Thompson, 2002) for effect sizes that failed the heterogeneity test.  

**RESULTS**

**Quality Assessment**

Twenty studies representing 13,551 participants were included in the final body of evidence (Table 1 and Appendix Table 6).
Eleven studies examined the effectiveness of self- or clinically applied fluoride. Of these studies, 10 were randomized clinical trials, and 1 was a controlled trial (split-mouth) that did not specify whether the treatment had been randomly assigned. Nine studies examined the effectiveness of water fluoridation—one was a prospective cohort trial that examined caries increment among randomly selected lifelong residents of fluoridated and non-fluoridated communities, and 8 were cross-sectional studies. In this last group, 7 compared caries prevalence between lifelong residents of fluoridated and non-fluoridated communities, and 1 used linear regression analysis to estimate average caries increment attributable to 1 yr of exposure to water fluoridation. Among the 12 longitudinal studies, 9 reported the drop-out rate (mean drop-out rate for one yr [weighted by sample size] = 10.9%), 5 reported that examiners were blinded, and 8 reported using a placebo.

**Is Any Fluoride Effective in Preventing Caries?**

Eighteen studies (11,649 participants) compared coronal caries among adults of all ages by fluoride exposure (Table 2). Caries was always higher in the control group than in the treatment group. With Fisher's inverse chi-square method, the combined p-values were less than 0.001. Six studies (2290 participants) compared coronal caries among adults aged 40+ yrs. Again, caries was always higher in the control group than in the treatment group, and the combined p-values were less than 0.001. Finally, 7 studies (2112 participants) compared root caries among adults aged 40+ yrs by fluoride exposure (Table 2); in all studies, caries was higher in the non-fluoride than in the fluoride group, and the combined p-values were less than 0.001.

**How Effective is Community Water Fluoridation in Preventing Caries?**

The combined results of the 9 studies (7853 participants) examining the effectiveness of water fluoridation were significant at p < 0.001 (Table 2). Among the 7 studies including only lifelong residents of control or fluoridated-water communities (5409 participants; Appendix Table 8 and Appendix Fig. 2), the summary relative risk ratio was 0.654 (95% confidence interval [CI]: 0.490-0.874); this is equivalent to a prevented fraction of 34.6% (95%CI: 12.6%-51.0%). Heterogeneity was present. Heterogeneity was not an issue when we pooled the 5 fluoridation studies published after 1979 (2530 participants); the summary-prevented fraction was 27.2% (95%CI: 19.4%-34.3%).

**How Effective are the Different Modes of Fluoride in Preventing Caries?**

The difference in annual coronal caries increment between exposed and not-exposed adults of all ages for all modes of fluoride delivery ranged from 0.02 to 2.17 surfaces (11 studies with 4809 participants; Fig. 1). The summary difference was 0.64 surfaces (95%CI: 0.35-0.94). Heterogeneity was present. There were enough studies to estimate an effect measure for studies published during/after 1980 (6 studies with 3573 participants). The summary difference in annual caries increment for these studies was 0.29 coronal surfaces (95%CI: 0.16-0.42). Both the chi-square test, p > 0.05, and the I² test, 0.38, indicated that heterogeneity was not an issue.

The difference in annual root caries increment by any fluoride exposure for adults aged 40+ ranged from 0.05 to 0.50 (5 studies all published after/during 1980, with 1894 participants; Fig. 2). The summary difference was 0.22 (95%CI: 0.08-0.37). Both the chi-square test, p > 0.05, and the quantity I², equaling 0.15, indicated that heterogeneity was not significant.

For self-applied fluoride, the difference in annual coronal caries increment between exposed and not-exposed adults ranged from 0.02 to 2.17 (Appendix Fig. 3; 7 studies with 3503 participants). The summary difference was 0.72 (95%CI: 0.20-1.24). Heterogeneity was present. When we restricted the analysis to the 5 studies that included solely self-applied fluoride (3049 participants), the summary difference decreased to 0.30 surfaces (95%CI: 0.09 to 0.51). Although the chi-square test indicated that heterogeneity was not an issue, the quantity I² indicated that about 53% of the difference among studies was due to heterogeneity as opposed to random chance.

Because only 2 studies examined the effectiveness of professionally applied fluoride without another fluoride modality, we did not calculate summary measures for this mode of delivery.

**DISCUSSION**

One limitation of this review is the quality and the quantity of studies on fluoride effectiveness among adults. Recent meta-analyses of fluoride rinses and toothpastes among children...
Figure 1. Absolute reduction in coronal caries increment that was attributed to fluoride exposure. *Indicates study published during or after 1980.

Values to the right of the 'no effect' line (difference in caries increment is positive) indicate fluoride effective, and values to the left (negative difference) indicate fluoride ineffective.

- Community water fluoridation.
- Self-applied fluoride.
- Combination of self-applied and professionally applied fluoride.
- Professionally applied fluoride.

Figure 2. Absolute reduction in root caries increment attributed to fluoride exposure. *Indicates study published during or after 1980.

Values to the right of the 'no effect' line (difference in caries increment is positive) indicate fluoride effective, and values to the left (negative difference) indicate fluoride ineffective.

- Community water fluoridation.
- Self-applied fluoride.
- Combination of self-applied and professionally applied fluoride.

included 36 and 74 randomized or quasi-randomized controlled trials (Marinho et al., 2003a,b), respectively, whereas this review could locate only 8 such studies from which to estimate the size of the effect. Because of the paucity of studies, we were not able to exclude studies without blind outcome assessment, as was done in the recent meta-analysis for children. In addition, our findings on the effectiveness of self-applied fluoride may not be generalizable to the current generation of adults; there were only 4 studies published after 1979 (the summary measure, however, was significant). Finally, we also included cross-sectional studies to evaluate water fluoridation. Thus, there is a clear need for further well-designed studies on the effectiveness of fluoride among adults.

One interesting finding, however, was the consistency of the effect size for the various modes of fluoride delivery among adults, and their similarity to findings for children. Using findings from studies published after 1979, and assuming that the annual coronal caries increment among adults is 1 surface (Griffin et al., 2005), we found that exposure to any mode of fluoride reduced caries by about 25%. This value is similar to the prevented fraction for community water fluoridation. When we restricted the analysis of the effect of self-applied fluoride to 4 studies published after 1979, the prevented fraction again equaled 25% (data not shown). A recent meta-analysis conducted among children and youth also found preventive fractions of fluoride rinse (26%) and toothpaste (24%) close to 25% (Marinho et al., 2003a,b).

On a population basis, caries is becoming a more important health issue among adults, especially older adults, because they are more likely to retain their natural teeth than in previous generations. A comparison of the National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1994 with that conducted in 1999-2002 indicates that the mean number of missing teeth among adults aged 40+ has decreased by 22% (Beltran-Aguilar et al., 2005). In addition, the percentage of the population that is older is increasing. Thus, there are more at-risk teeth, making population-based efforts at prevention even more important.

Although adults are as likely to experience new caries as children, certain segments of the U.S. adult population—those with low incomes and the elderly—may have little or no access to restorative or preventive clinical care. At present, approximately 15% of state Medicaid programs provide no adult dental benefits at all, and approximately 45% cover only tooth extraction and emergency services (Oral Health America, 2003). Routine dental care is one of the few health areas not covered by Medicare. Limited access to restorative care increases the need for effective prevention; complications and
Fluoride Affects Adults

pains and suffering are more likely if caries remains untreated.

The proportion of the U.S. population comprised of older adults is increasing, most of these persons are likely to be dentate and at risk for dental caries, and many lower-income adults lack access to timely restorative care. Our finding that fluoride is effective among all adults supports the development and implementation of fluoride programs to serve this population.

ACKNOWLEDGMENTS

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REFERENCES


A Bayesian analysis of multivariate doubly-interval-censored dental data

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SUMMARY
A Bayesian survival analysis is presented to examine the effect of fluoride-intake on the time to caries development of the permanent first molars in children between 7 and 12 years of age using a longitudinal study conducted in Flanders. Three problems needed to be addressed. Firstly, since the emergence time of a tooth and the time it experiences caries were recorded yearly, the time to caries is doubly interval censored. Secondly, due to the setup of the study, many emergence times were left-censored. Thirdly, events on teeth of the same child are dependent. Our Bayesian analysis is a modified version of the intensity model of Härkänen et al. (2000, Scandinavian Journal of Statistics 27, 577–588). To tackle the problem of the large number of left-censored observations a similar Finnish data set was introduced. Our analysis shows no convincing effect of fluoride-intake on caries development.

Keywords: Bayesian analysis; Intensity models; Multivariate doubly-interval-censored data.

1. RESEARCH QUESTION AND COLLECTED DATA
In this paper, we present a Bayesian analysis of a longitudinal dental data set (the Signal Tandmobiel® study) to tackle the following research question: Does fluoride-intake at a young age have a protective effect on caries in permanent teeth? Our analyses will be limited to the caries experience of the four permanent first molars (teeth number 16, 26, 36, 46 in European dental notation).

In this study, detailed oral health data at tooth and tooth-surface level (caries experience, gingivitis, etc.) from 4468 Flemish schoolchildren (2315 boys and 2153 girls) born in 1989 were collected annually between 1996 and 2001. The children were cluster-sampled from randomly chosen Flemish schools. Two stratification factors, geographical location (five provinces) and educational system (three school systems), were taken into account. Further details on the design of the study can be found in Vanobbergen et al. (2000).

*To whom correspondence should be addressed.
Our data suggest that the use of fluoride reduces caries experience in primary teeth, see Vanobbergen et al. (2001) and that fluoride-intake delays the emergence of the permanent teeth, see Leroy et al. (2003). The latter result raises the question whether the fluoride-intake only reduces the time at risk or whether it has also a direct protective effect on caries experience.

Unfortunately, fluoride-intake in children cannot be measured accurately. Indeed, fluoride-intake can come from: (1) fluoride supplements (systemic), (2) accidental ingestion of toothpaste or (3) tap water. Further, the intake from these sources can be recorded only crudely. Therefore, it was decided to measure fluoride-intake by the degree of fluorosis on some reference teeth. Fluorosis is the most common side-effect of fluoride-intake and appears as white spots on the enamel of teeth. For this analysis, a child was considered fluoride-positive (covariate fluor = 1) if there were white spots on at least two permanent maxillary incisors during the fourth year of the study or during both the fifth and sixth year of the study.

The prevalence of fluorosis was relatively low (480 children, 10.8%). In our analysis, 480 fluorosis children and 960 randomly selected fluorosis-free children are included. Case-control subsampling was done to reduce computation time. To check that it did not destroy the stratification, we constructed a 5 × 3 × 2 contingency table with factors province, school system and whether the child is in the subsample or not (subsample). A p-value of 0.13 was obtained for the significance of the interaction of the third factor with the other two using a likelihood-ratio test in a log-linear model, implying that the stratification is similar in the used and the discarded subsamples.

The prevalence of caries experience at the age of 12 was negligible (at most 1.4%) for all permanent teeth except for the first molars (teeth used in the analysis). For these teeth, the prevalence was 25.8% in children with fluorosis compared to 29.4% in fluorosis-free children, with prevalence of 23.3% and 27.7% for boys, and 27.9% and 31.2% for girls, respectively. Thus, at first sight, the impact of fluoride-intake seems to be minor. However, since the emergence of permanent teeth might be delayed by fluoride-intake, evaluating the impact of fluoride-intake should take into account the time at risk for caries. Hence, in our analysis, the response will be the time between emergence and the onset of caries development. But both tooth emergence and onset of caries development are interval-censored, implying a doubly-interval-censored response. See Figure 1 for a graphical illustration of a possible evolution of a particular tooth.

At the onset of the study, about 86% of the permanent first molars had already emerged. The severity of this censoring will affect the efficiency with which the effect of fluoride-intake can be estimated. We tried two strategies to improve the efficiency of our estimation procedure. First, we included in our analysis the
Table 1. Naive Proportional Hazards Models. Hazard ratios (95% confidence intervals (CI)) between a fluorosis and fluorosis-free group of children while controlling for gender and jaw emergence times of teeth 14, 24, 34, 44, 12, 22, 33, 43 all of which had emerged in more than 60% of cases during the course of the study. By incorporating information on these teeth and using the association between teeth of the same subject (via the concept of ‘the birth time of dentition’, see next section), it was attempted to estimate the true emergence time of the permanent first molars better. Second, emergence times from a Finnish longitudinal data set (Virtanen, 2001), involving 235 boys and 223 girls born in 1980–81 with follow-up from 6 to 18 years, were added to our Flemish data. For these Finnish data, almost all 28 permanent teeth emerged during the study period.

Our research question is not uncommon in dentistry but cannot be addressed within any classical statistical package. For our analysis, we have used the software package BITE (Härkänen, 2003), based on a non-parametric Bayesian survival model developed by Härkänen et al. (2000). Section 2 presents a frequentist Cox proportional hazards (PH) regression model using the midpoints of the observed intervals as if they were exact observations, to compare our Bayesian model to a more commonly used approach. In the third section, the Bayesian model suggested by Härkänen et al. (2000) and modified for our purposes is explained. Results are presented in Section 4. Section 5 is a discussion of our methods.

2. PROPORTIONAL HAZARDS MODELS USING MIDPOINTS

A standard frequentist Cox proportional hazards (PH) model (Cox, 1972) could be applied, replacing interval-censored observations by the midpoints of the observed intervals and treating the resulting data as right-censored observations. In this way, we analyzed time to caries development for the four permanent first molars. For our analysis, the left-censored emergence times were first assumed to be interval-censored with a lower limit for emergence of 5 years, which is practically the youngest age for the emergence of these teeth (Nanda, 1960). Possible dependencies between the four teeth of the same child can be taken into account, for example by inclusion of a Gamma-distributed frailty component in the model (see Hougaard, 2000).

Based on preliminary Bayesian modelling, we do not distinguish between opposite teeth in the same jaw (horizontal symmetry). However, we do make a distinction between maxillary (upper) and mandibular (lower) teeth and also between teeth in different positions (of a quadrant) in the mouth.

For comparison purposes, we present the same PH model as the one shown here but analyzed by Bayesian methods. Hence, the hazard for the time to caries of the $j$th tooth of the $i$th child depends on the tooth position, fluor and gender of the child ($0 = \text{boy, } 1 = \text{girl}$). More specifically,

$$
\lambda(t | \text{tooth}_j, \text{gender}_i, \text{fluor}_i) = \lambda_0(t) \cdot Z_i \cdot \exp(\beta^T x_{ij}),
$$

where $\lambda_0(t)$ is an unspecified baseline hazard function, $\beta = (\beta_1, \ldots, \beta_5)^T$, and $x_{ij} = (\text{fluor}_i, \text{gender}_i, \text{tooth}_j, \text{fluor}_i \times \text{gender}_i, \text{fluor}_i \times \text{tooth}_j)^T$. The covariate ‘tooth’ is a dummy variable that distinguishes teeth in different positions in the mouth (apart from
horizontal symmetry). The term $Z_i$ is either one, corresponding to a model without frailties or a Gamma-distributed frailty term.

Estimates of hazard ratios between the fluorosis and fluorosis-free group controlling for gender and jaw are shown in Table 1. As seen, incorrectly ignoring dependencies between the responses of one child by using a model without frailties artificially decreases the size of the confidence interval. Although both models conclude that the effect of fluorosis on the development of caries on the permanent first molars is at the borderline of 5% significance (Table 1), the results are not reliable. Law and Brookmeyer (1992) have pointed out that the statistical properties of midpoint imputation depend strongly on the underlying distribution of the event times. For that reason, a more sophisticated analysis is needed.

3. The Bayesian survival model for interval-censored data

The non-parametric Bayesian intensity model of Härkänen et al. (2000) provides a flexible tool for analyzing multivariate survival data. Further, a software package written in C, called BITE (downloadable from http://www.rni.helsinki.fi/~tth together with scripts used to perform all analyses presented here), makes the analysis feasible in practice.

3.1 Model for emergence

Let $a_{ij}$ be the (unknown) age at which tooth $j$ of child $i$ emerged. The hazard for emergence at time $t$ is

$$\lambda_{ij}(t) = f(t - \eta_i|\text{tooth}_j, \text{gender}_i) \times I[\eta_i < t \leq a_{ij}].$$

The dependence between emergence times of one child is accounted for by using a subject-specific variable $\eta_i$ called birth time of dentition. This is a latent variable which represents the common time marking the onset of the tooth eruption process and hereby 'explains' the positive correlation between eruption times $a_{ij}$ within a subject. Note that $\eta_i$ is practically always less than the first emergence time of the permanent teeth. The intensity of emergence for a particular child is zero before that time, expressed by the indicator $I[\eta_i < t \leq a_{ij}]$. The hazard function $f(\cdot|\text{tooth}_j, \text{gender}_i)$ is defined as piece-wise constant for estimation purposes.

3.2 Model for caries experience

Let $b_{ij}$ be the age at which the $j$th tooth of child $i$ developed caries. The hazard for the caries process is given by

$$\lambda_{ij}^{(c)}(t) = Z_i \times h(t - a_{ij}|\text{tooth}_j, \text{gender}_i, \text{fluor}_i) \times I[a_{ij} < t \leq b_{ij}],$$

where the variable $Z_i$ is an unknown subject-specific frailty coefficient modulating the hazard function. Again, we assume in (3) that $h$ is piece-wise constant. We call the difference $b_{ij} - a_{ij}$ the caries experience-free time.

The covariate ‘fluor’ will be used in two ways. First, for each combination of values of fluor, gender and tooth, a piece-wise constant hazard function is specified and fitted. Second, the term $h(\cdot|\text{tooth}_j, \text{gender}_i, \text{fluor}_i)$ in (3) is replaced by $h(\cdot) \times \exp(\beta^T x_{ij})$, with $\beta$ and $x_{ij}$ being the same as in (1), thus assuming a PH model for caries experience whilst retaining a piece-wise constant baseline hazard function $h(\cdot)$.
3.3 Remarks

Our statistical model will involve the above two measurement models. Hence, the possible dependencies among times of interest are taken into account by involving two types of subject-specific parameters, \( \eta_i \) and \( Z_i \). The first subject-specific parameter \( \eta_i \) is included in the model for the emergence and will shift the hazard function in time, whereas the frailty \( Z_i \) recognizes that the teeth of one child can be more sensitive to caries than the corresponding teeth of another child, reflecting different dietary behavior, brushing habits, etc.

3.4 Priors for baseline hazard functions

In BITE, the working assumption is that hazard functions are piece-wise constant. Further, for the emergence hazard functions \( f(\cdot|\text{tooth}_j, \text{gender}_i) \), the first level of the piece-wise constant and the increment levels are assigned Gamma prior distributions. This will ensure a priori an increasing hazard function for emergence. In the case of caries experience, the first level of the piece-wise constant hazard function, say \( h_0 \), is assigned a Gamma prior distribution. Further, the level \( h_m \) of the \( m \)th interval has, conditional on the previous levels \( h_0, \ldots, h_{m-1} \), a Gamma(\( \alpha, \alpha/h_{m-1} \)) prior distribution. This gives a priori \( E[h_m|h_{m-1}, \ldots, h_0] = h_{m-1} \) and ensures that there is no built-in prior assumption of trend in the hazard rate. Finally, the prior for the jump points of each piece-wise constant function is a homogeneous Poisson process, as suggested by Arjas and Gasbarra (1994). Because jump points are assumed to be random and not fixed, the posterior predictive hazard functions will be smooth, rather than piece-wise constant.

3.5 Priors for the random effect terms

The prior distribution for the birth time of dentition \( \eta_i \) illustrates how we have combined the Flemish data and the Finnish data and how the timing of emergence of the Finnish data is included in our analysis. We assume that the shapes of the emergence hazard functions \( f \) for Finland and Flanders are the same but we do allow for a shift in emergence times by assuming different means for the birth time of dentition in the two countries. More precisely, the prior distribution of \( \eta_i \) is assumed normal \( N(\xi_0, \tau^{-2}) \) for a Finnish child and normal \( N(\xi_1, \tau^{-2}) \) for a Flemish child. The Bayesian approach allows us to include the dentist’s knowledge on the problem at hand by assigning to the parameters \( \xi_0 \) and \( \xi_1 \) independent normal prior distributions with mean 5.2 years and standard deviation 1 year. Both the normal distribution as well as the choice of the prior means and standard deviation of the hyperparameters \( \xi_0 \) and \( \xi_1 \) are motivated by the results found in the literature on the earliest emergence of permanent teeth (see Nanda, 1960 or, more recently, Parner et al., 2001). This reflects the dentist’s belief that permanent teeth, on average, emerge slightly after 5 years of age. The parameter \( \tau^2 \) is assigned a Gamma(2, 2) prior distribution.

The individual frailties \( Z_i \) in the model for caries are a priori assumed to be conditional on the hyperparameter \( \phi \), independent and identically Gamma-distributed with both shape and inverse scale equal to that hyper-parameter. The hyper-parameter itself is then given a Gamma(2, 2) prior distribution. Sensitivity of the results with respect to the choice of parameters for priors of hyperparameters \( \xi_0, \xi_1, \tau \) and \( \phi \) will be discussed in Section 4.

3.6 Treatment of censored data

Left- and interval-censoring are treated by data augmentation (Tanner and Wong, 1987). First, the left-censored emergence times of all teeth are changed into interval-censored emergence times with a lower
limit equal to 4 years, implying that less internal information is used here than previously with the frequentist PH model where the limit was 5 years. In the case that both emergence and caries development were observed within one observational interval, we force sampled values of the Markov Chain Monte Carlo (MCMC) to satisfy $b_{ij} > a_{ij}$.

### 3.7 Bayes inference on model components

The posterior distributions based on the model with prior assumptions described in the previous paragraphs are minor modifications of those derived in Härkänen et al. (2000). Our Bayesian model is complex and requires the use of MCMC sampling techniques (Gilks et al., 1996). The software package BITE (Härkänen, 2003), based on the Metropolis–Hastings algorithm (Metropolis et al., 1953; Hastings, 1970), was used to sample from the posterior distributions. Further, BITE employs the reversible jump approach of Green (1995) to sample piece-wise constant hazard functions. We carried out two runs, each with 20,000 iterations of burn-in followed by 14,000 iterations with a 1:4 thinning to obtain a sample from the posterior distribution. We used the Gelman and Rubin (1992) test to check for convergence.

### 4. Results

#### 4.1 A non-parametric model with Flemish and Finnish data

To evaluate the effect of fluoride-intake on the development of caries on the permanent first molars, we have calculated the posterior expectations of hazard ratios $h(t|\text{tooth}, \text{gender}, \text{fluorosis}) / h(t|\text{tooth}, \text{gender}, \text{fluorosis-free})$. These hazard ratios together with their 95% equal-tail point-wise credibility intervals can be found in Figure 2. The PH assumption with respect to covariate $\text{fluor}$ seems to be satisfied since credibility intervals in all cases cover a horizontal line. In three cases, this horizontal line is close to the dotted–dashed line $y = 1$ implying no effect of fluoride-intake on caries development. A positive effect of fluoride-intake seems to be present only for mandibular permanent first molars in boys. There are also no deviations from the PH assumption with respect to $\text{gender}$ and $\text{tooth}$ (plots are not shown). This allowed us to assume for the caries model a PH effect of the three covariates, possibly including some interaction terms. By this semi-parametric assumption, it was hoped to see more clearly the effect of fluoride-intake on caries experience.

#### 4.2 A proportional hazards model with Flemish and Finnish data

For the reasons stated in the previous paragraph, we have fitted a model where the caries hazard function (3) was changed into

\[
\lambda^{(c)}_{ij}(t) = Z_i \times h(t) \times \exp(\beta^T x_{ij}) \times I[a_{ij} < t \leq b_{ij}],
\]

where $x_{ij}$ and $\beta$ are same as in (1). The additional $\beta$-parameters were given an $\text{N}(0, 10^2)$ prior. However, the hazard function for emergence is still defined by (2). Posterior expectations of the hazard ratios between the fluorosis groups while controlling for the other covariates are given in the left-hand part of Table 2.

The PH analysis for caries gives similar conclusions to the previous non-parametric analysis. A positive effect of fluoride-intake is now seen for the mandibular permanent first molars of boys and has a borderline positive effect for the maxillary permanent first molars of boys. However, no effect of fluoride-intake was seen for girls.
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Fig. 2. Bayesian Non-Parametric Model based on Flemish and Finnish Data. Posterior means of the hazard ratios between the fluorosis groups (solid curve), 95% point-wise equal-tail probability region (dashes).

Table 2. Bayesian Proportional Hazards Models. Hazard ratios (95% equal-tail credibility intervals (CI)) between fluorosis groups while controlling for gender and jaw for models fitted using both Flemish and Finnish data and Flemish data only

<table>
<thead>
<tr>
<th>Group</th>
<th>Flemish and Finnish data</th>
<th>Flemish data only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poster. mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Boys, maxilla</td>
<td>0.674 (0.492, 1.010)</td>
<td>0.651 (0.463, 0.960)</td>
</tr>
<tr>
<td>Boys, mandible</td>
<td>0.991 (0.721, 1.364)</td>
<td>1.002 (0.698, 1.333)</td>
</tr>
</tbody>
</table>

4.3 Remark concerning hyperparameters

The posterior expectations and 95% equal-tail credibility intervals of the hyperparameters related to the birth times of dentition \( \eta_i \) and frailties \( Z_i \) are given in the upper part of Table 3. The non-parametric model and PH model for caries give similar results.

We now state our conclusions concerning the emergence process in Flanders and Finland. The emergence process starts slightly earlier in Finland (by approx. 0.2 years) than in Flanders, as is seen by the difference in the posterior expectations of the means of birth time of dentition. The MCMC output for the hyperparameters can also be used to estimate properties of the predictive distributions of birth time.
Table 3. Bayesian Models with Flemish and Finnish Data. Posterior means and 95% equal-tail credibility intervals for the hyperparameters: \( \mu_0 \), conditional expectation of \( \eta_i \) for Finland; \( \mu_1 \), conditional expectation of \( \eta_i \) for Flanders; \( \tau^{-2} \), conditional variance of \( \eta_i \); \( \phi^{-1} \), conditional variance of frailties \( Z_i \) (top of the Table). Means of the posterior predictive distributions and 95% equal-tail posterior predictive intervals for the birth time of dentition \( \eta_i \) in Finland and Flanders, respectively, and for the frailty term \( Z_i \) (bottom of the table)

<table>
<thead>
<tr>
<th>Hyperparameter</th>
<th>Non-parametric model</th>
<th>Cox regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_0 )</td>
<td>5.47 (5.40, 5.54)</td>
<td>5.45 (5.38, 5.52)</td>
</tr>
<tr>
<td>( \mu_1 )</td>
<td>5.69 (5.64, 5.73)</td>
<td>5.68 (5.64, 5.73)</td>
</tr>
<tr>
<td>( \tau^{-2} )</td>
<td>0.48 (0.45, 0.52)</td>
<td>0.49 (0.45, 0.52)</td>
</tr>
<tr>
<td>( \phi^{-1} )</td>
<td>3.85 (3.57, 4.17)</td>
<td>3.94 (3.58, 4.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-parametric model</th>
<th>Cox regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \eta_i ) (Finland)</td>
<td>5.48 (4.12, 6.79)</td>
<td>5.45 (4.05, 6.84)</td>
</tr>
<tr>
<td>( \eta_i ) (Flanders)</td>
<td>5.69 (4.33, 7.09)</td>
<td>5.69 (4.34, 7.01)</td>
</tr>
<tr>
<td>( Z_i )</td>
<td>1.02 (10^{-6}, 6.90)</td>
<td>0.95 (10^{-6}, 6.45)</td>
</tr>
</tbody>
</table>

of dentition and frailties. Their means and 95\% equal-tail posterior predictive intervals are shown in the bottom part of Table 3, which shows that the average of Finnish birth time of dentition is close to 5.5 years of age, slightly higher than the prior expectation but close to the value obtained by Härkänen et al. (2000) on another Finnish data set. The 95\% posterior predictive intervals show that the actual moment of birth time of dentition varies between about 4 and 7 years of age. Finally, the 95\% posterior predictive interval of \( Z_i \) shows a clear heterogeneity in the frailty for caries experience.

4.4 Sensitivity analysis

First, model (4) was fitted using Flemish data only, to see how influential the inclusion of the Finnish data was. As seen in Table 2, the hazard ratios changed only slightly. The same was true for the remaining parameters. Moreover, the Finnish data improved only slightly the precision with which the emergence of the first permanent molars was estimated.

To see how the behavior of the parameter estimates changes when informative priors for the hyperparameters are modified, we have fitted the proportional hazards model with Flemish data only, using different choices of priors for the hyperparameters. Specifically, we used normal distributions \( N(3, 2) \), \( N(4, 1) \), \( N(5.2, 1) \), \( N(6, 1) \) as priors for the expectation \( \xi_0 \) of birth time of dentition \( \eta_i \). The standard deviation of the normal prior with mean 3 years was increased so as to cover realistic emergence times of permanent teeth. We used Gamma(0.1, 0.1), Gamma(2, 2) and Gamma(10, 10) distributions as priors for the precision \( \tau \) of the variance of the birth time of dentition and for the precision \( \phi \) of frailties \( Z_i \). All other parameters were given flat priors and there is, thus, no reason to modify them.

Posterior means and 95\% equal-tail credibility intervals for hazard ratios between the fluorosis and fluorosis-free groups for different choices of the prior distributions are shown in Figure 3, which shows that the influence of the choice of the prior distribution is not strong.

We argue that our other assumptions are not strong. Indeed, we only assume that the distributions of the birth time of dentition differ between Finnish and Flemish populations only in their means. Moreover, as indicated earlier, the Finnish data had only a slight impact on the results for the Flemish data. Further,
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5. DISCUSSION

The model presented here allows for the analysis of survival data in dental research where interval-censored data and dependencies between observations (e.g. between teeth in the same mouth) are common. Our specific application is to a typical dental research question, i.e. whether fluoride-intake has a protective effect for caries. The results show that the protective effect of fluoride-ingestion is not convincing. We observed a positive effect only for mandibular teeth of boys. This agrees with current guidelines for the use of fluoride in caries prevention, where only the topical application (e.g. fluoride in tooth paste) is considered to be essential (Oulis et al., 2000).

We acknowledge that our analyses could have been more refined if the amount of left- and right-censoring was less, for instance if the study had started approximately one year earlier and ended in high school. This would make our analyses less dependent on prior assumptions. Yet these prior assumptions are simply a reflection of basic dental knowledge and it would be a waste not to use them. Moreover, to our knowledge, the Signal Tandmobiel® trial is possibly the largest longitudinal study executed with such great detail on dental aspects.
This paper has illustrated the usefulness of our Bayesian approach, i.e. the possibility to incorporate prior information and to relax the parametric assumptions often made in survival analysis with interval-censored data. However, our approach is computationally demanding. On a Pentium IV 2 GHz PC with 512 MB RAM, one BITE run took about 5 days to converge. However, in an epidemiological analysis where there is correlation among the subjects, where the response and/or the covariates are (right-, left- or interval-) censored and when we wish to avoid parametric assumptions, we doubt any classical approach will suffice. Furthermore, the BITE package of Härkänen (2003) gave us the possibility to avoid the specification of a parametric model. We, therefore, would recommend this package for hard problems in survival analysis.

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Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis

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Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis

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Key Words: Fluoride, Intelligence, Neurotoxicity

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The authors declare that they have no competing financial interest.

List of Abbreviations:

CI, confidence interval

CNKI, China National Knowledge Infrastructure

SE, standard error

SMD, Standardized mean difference

TOXNET, Toxicology Data Network
Abstract

**Background:** Although fluoride may cause neurotoxicity in animal models and acute fluoride poisoning causes neurotoxicity in adults, very little is known of its effects on children’s neurodevelopment.

**Objective:** We performed a systematic review and meta-analysis of published studies to investigate the effects of increased fluoride exposure and delayed neurobehavioral development.

**Methods:** We searched the MEDLINE, EMBASE, Water Resources Abstracts, and TOXNET databases through 2011 for eligible studies. We also searched the China National Knowledge Infrastructure (CNKI) database, as many studies on fluoride neurotoxicity have been published in Chinese journals only. In total, we identified 27 eligible epidemiological studies with high and reference exposures, endpoints of IQ scores or related cognitive function measures with means and variances for the two exposure groups. We estimated the standardized mean difference (SMD) between exposed and reference groups across all studies using random effects models. We conducted sensitivity analyses restricted to studies using the same outcome assessment and having drinking water fluoride as the only exposure. Cochran test for heterogeneity between studies, Begg’s funnel plot and Egger test to assess publication bias were performed. Meta-regressions to explore sources of variation in mean differences among the studies were conducted.

**Results:** The standardized weighted mean difference in IQ score between exposed and reference populations was -0.45 (95% CI -0.56 to -0.35) using a random-effects model. Thus, children in high fluoride areas had significantly lower IQ scores than those who lived in low fluoride areas. Subgroup and sensitivity analyses also indicated inverse associations, although the substantial heterogeneity did not appear to decrease.
Conclusions: The results support the possibility of an adverse effect of high fluoride exposure on children’s neurodevelopment. Future research should include detailed individual-level information on prenatal exposure, neurobehavioral performance, and covariates for adjustment.
Introduction

A recent report from the US National Research Council (NRC 2006) concluded that adverse effects of high fluoride concentrations in drinking-water may be of concern and that additional research is warranted. Fluoride may cause neurotoxicity in laboratory animals, including effects on learning and memory (Chioca et al. 2008; Mullenix et al. 1995). A recent experimental study where the rat hippocampal neurons were incubated with various concentrations (20 mg/L, 40 mg/L, and 80 mg/L) of sodium fluoride in vitro showed that fluoride neurotoxicity may target hippocampal neurons (Zhang et al. 2008). Although acute fluoride poisoning may be neurotoxic to adults, most of the epidemiological information available on associations with children’s neurodevelopment is from China, where fluoride generally occurs in drinking water as a natural contaminant, and the concentration depends on local geological conditions. In many rural communities in China, populations with high exposure to fluoride in local drinking water sources may reside in close proximity to populations without high exposure (NRC 2006).

Opportunities for epidemiological studies depend on the existence of comparable population groups exposed to different levels of fluoride from drinking water. Such circumstances are difficult to find in many industrialized countries, as fluoride concentrations in community water are usually no higher than 1 mg/L, even when fluoride is added to water supplies as a public health measure to reduce tooth decay. Multiple epidemiological studies of developmental fluoride neurotoxicity were conducted in China due to the high fluoride concentrations that are substantially above 1 mg/L in well-water in many rural communities, although microbiologically safe water has been accessible to many rural households as a result of the recent five-year plan (2001-2005) by the Chinese government. It is projected that all rural
residents will have access to safe public drinking water by 2020 (World Bank 2006). However, results of the published studies have not been widely disseminated. Four studies published in English (Li et al. 1995; Lu et al. 2000; Xiang et al. 2003; Zhao et al. 1996) were cited in a recent report from the National Research Council (NRC 2006), while the World Health Organization has considered only two (Li et al. 1995; Zhao et al. 1996) in its most recent monograph on fluoride (WHO 2002).

Fluoride readily crosses the placenta (ATSDR 2003). Fluoride exposure to the developing brain, which is much more susceptible to injury caused by toxicants than is the mature brain, may possibly lead to damage of a permanent nature (US EPA 2011). Based on the considerations of health risks, and in response to the recommendation of the National Research Council (NRC 2006), the U.S. Department of Health and Human Services (HHS) and the U.S. Environmental Protection Agency (EPA) recently announced that HHS is proposing to change the recommended level of fluoride in drinking water to 0.7 mg/L from the currently recommended range of 0.7 to 1.2 mg/L, and EPA is reviewing the maximum amount of fluoride allowed in drinking water, which currently is set at 4.0 mg/L (US EPA 2011).

To summarize the available literature, we performed a systematic review and meta-analysis of published studies on increased fluoride exposure in drinking water and neurodevelopmental delays. We specifically targeted studies carried out in rural China that have not been widely disseminated, thus complementing the studies that have been included in previous reviews and risk assessment reports.
Methods

Search Strategy

We searched MEDLINE (National Library of Medicine, Bethesda, MD; http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (Elsevier B.V., Amsterdam, the Netherlands; http://www.embase.com), Water Resources Abstracts (Proquest, Ann Arbor, MI; http://www.csa.com/factsheets/water-resources-set-c.php), and TOXNET (National Library of Medicine, Bethesda, MD; http://toxnet.nlm.nih.gov) databases to identify studies of drinking water fluoride and neurodevelopmental outcomes in children. In addition, we searched the China National Knowledge Infrastructure (CNKI; http://www.cnki.net) database to identify studies published in Chinese journals only. Keywords included combinations of “fluoride” or “drinking water fluoride”, “children”, “neurodevelopment” or “neurologic” or “intelligence” or “IQ”. We also used references cited in articles identified. Records were searched from 1980 to 2011. Our literature search identified 39 studies, among which 36 (95%) were studies with high and reference exposure groups, and 3 (7.7%) studies were based on individual-level measure of exposures. The latter showed dose-related deficits were found but were excluded because our meta-analysis focused on studies with the high and low exposure groups only. In addition, 2 studies were published twice, and the duplicates were excluded.

Inclusion criteria and Data Extraction

The criteria for inclusion of studies included studies with high and reference fluoride exposures, endpoints of IQ scores or other related cognitive function measures, presentation of a mean outcome measure and associated measure of variance [95% confidence intervals (CI) or standard errors (SEs) and numbers of participants]. Interpretations of statistical significance are based on
an alpha level of 0.05. Information included for each study also included the first author, location of the study, year of publication, and numbers of participants in high-fluoride and low-fluoride areas. We noted and recorded the information on age and gender of children, and parental education and income if available.

**Statistical Analysis**

STATA (version 11.0; StataCorp, College Station, TX) and available commands (Stern 2009) were used for the meta-analyses. A standardized weighted mean difference (SMD) was computed using both fixed-effects and random-effects models. The fixed-effects model uses the Mantel-Haenszel method assuming homogeneity among the studies, while the random-effects model uses the DerSimonian and Laird method, incorporating both a within-study and an additive between-studies component of variance when there is between-study heterogeneity (Egger et al. 2001). The estimate of the between-study variation is incorporated into both the standard error of the estimate of the common effect and the weight of individual studies, which was calculated as the inverse sum of the within and between study variance. Heterogeneity among studies was evaluated using the $I^2$ statistic, which represents the percentage of total variation across all studies due to between-study heterogeneity (Higgins and Thompson 2002). The potential for publication bias was evaluated using Begg and Egger tests and visual inspection of a Begg funnel plot (Begg and Mazumdar 1994; Egger et al. 1997). We also conducted independent meta-regressions to estimate the contribution of study characteristics (mean age in years from the age range and year of publication in each study) to heterogeneity among the studies. The scoring standard for the Combined Raven’s Test – The Rural edition in China (CRT-RC) test classifies a score of $\leq 69$ and 70-79 as low and marginal intelligence,
respectively (Wang et al. 1989). We also used the random effects models to estimate risk ratios for the association between fluoride exposure and a low/marginal versus normal Raven’s test score among children in studies that used the Combined Raven’s Test –Rural in China (CRT-RC) test (Wang et al. 1989). Scores indicating low and marginal intelligence (≤69 and 70-79, respectively) were combined as a single outcome due to small numbers of children in each outcome subgroup.

Results

Six of the 34 studies identified were excluded due to missing information on the number of subjects or the mean and variance of the outcome (see Figure 1 for a study selection flow chart and Supplemental Material, Table S1 for additional information on studies that were excluded from the analysis). Another study (Trivedi et al. 2007) was excluded because SDs reported for the outcome parameter were questionably small (1.13 for high fluoride group, and 1.23 for low fluoride group) and the SMD (-10.8, 95% CI -11.9, -9.6) was more than 10-times lower than the second smallest SMD (-0.95, 95% CI -1.16, -0.75) and 150-times lower than the largest SMD (0.07, 95% CI -0.083, 0.22) reported for the other studies, which had relatively consistent SMD estimates. Inclusion of this study in the meta-analysis resulted with a much smaller pooled random-effects SMD estimate and a much larger $I^2 (-0.63 (95\% CI -0.83, -0.44), I^2 94.1\%$) compared to the estimates that excluded this study (-0.45, 95% CI -0.56, -0.34), $I^2 80\%$) (see Supplemental Material, Figure S1). Characteristics of the 27 studies included are shown in Table 1 (An et al. 1992; Chen et al. 1991; Fan et al. 2007; Guo et al. 1991; Hong et al. 2001; Li et al. 2003; Li et al. 2009; Li et al. 2010; Lin et al. 1991; Lin et al. 1994; Lin et al. 1995; Lu et al. 2000; Poureslami et al. 2011; Ren et al. 1989; Seraj et al. 2006; Sun et al. 1991; Wang et al.
1996; Wang et al. 2001; Wang et al. 2006; Wang et al. 2007; Xiang et al. 2003; Xu et al. 1994; Yang et al. 1994; Yao et al. 1996; Yao et al. 1997; Zhang et al. 1998; Zhao et al. 1996). Two of the studies included in the analysis were conducted in Iran (Poureslami et al. 2011; Seraj et al. 2006), otherwise the study cohorts were populations from China. Two cohorts were exposed to fluoride from coal burning (Guo et al. 1991; Li et al. 2010), otherwise populations were exposed to fluoride through drinking water. The CRT-RC was used to measure the children’s intelligence in 16 studies. Other intelligence measures included the Weschler Intelligence tests (3 studies), Binet IQ test (2 studies), Raven’s test (2 studies), Japan IQ test (2 studies), Chinese comparative intelligence test (1 study), and the mental work capacity index (1 study). As each of the intelligence tests used are designed to measure general intelligence, we used data from all eligible studies to estimate the possible effects of fluoride exposure on general intelligence.

In addition, we conducted a sensitivity analysis restricted to studies that used similar tests to measure the outcome (specifically, the CRT-RC, Weschler Intelligence test, Binet IQ test, or Raven’s test), and an analysis restricted to studies that used the CRT-RC. We also performed an analysis that excluded studies with co-exposures including iodine and arsenic, or with non-drinking water fluoride exposure from coal burning.

**Pooled SMD estimates**

Among the 27 studies, all but one study showed random-effect SMD estimates that indicated an inverse association, ranging from -0.95 (95% CI: -1.16, -0.75) to -0.10 (95% CI: -0.25, 0.04) (Figure 2). The study with a positive association reported a SMD estimate of 0.07 (95% CI: -0.8, 0.22). Similar results were found with the fixed-effect SMD estimates. The fixed-effects pooled SMD estimate and corresponding 95% CI were -0.40 (-0.44, -0.35), with a p-value <0.001 for
the test for homogeneity. The random-effects SMD estimate and 95% CI were -0.45 (95% CI: -0.56, -0.34) with an $I^2$ of 80% and homogeneity test p-value <0.001 (Figure 2). Because of heterogeneity (excess variability) between study results, we primarily used the random-effects model for subsequent sensitivity analyses, which is generally considered to be the more conservative method (Egger et al. 2001). Among the restricted sets of intelligence tests, the SMD for the model with only CRT-RC tests and drinking-water exposure (and to a lesser extent the model with only CRT-RC tests) was lower than that for all studies combined, although the difference did not appear to be significant. Heterogeneity, however, remained at a similar magnitude when the analyses were restricted (Table 2).

**Sources of heterogeneity**

We performed meta-regression models to assess study characteristics as potential predictors of effect. Information on the child’s gender and parental education were not reported in more than 80% of the studies, and only 7% of the studies reported household income. These variables were therefore not included in the models. Among the two covariates, year of publication (0.02; 95% CI: 0.006, 0.03), but not mean age of the study children (-0.02; 95% CI: -0.094, 0.04), was a significant predictor in the model with all 27 studies included. $I^2$ residual 68.7%, represented the proportion of residual between-study variation due to heterogeneity. From the adjusted $R^2$, 39.8% of between-study variance was explained by the two covariates. The overall test of the covariates was significant (p=0.004).

When the model was restricted to the 16 studies that used the CRT-RC, the child’s age (but not year of publication) was a significant predictor of the SMD. The $R^2$ of 65.6% of between-study variance was explained by the two covariates, and only 47.3% of the residual variation was due
to heterogeneity. The overall test of both covariates in the model remained significant ($p = 0.0053$). On further restriction of the model to exclude the 7 studies with arsenic and iodine as co-exposures and fluoride originating from coal-burning, thus including only the 9 with fluoride exposure from drinking water, neither age nor year of publication was a significant predictor, and the overall test of covariates was less important ($p = 0.062$), in accordance with the similarity of intelligence test outcomes and the source of exposure in the studies included. Although official reports of lead concentrations in the study villages in China were not available, some studies reported high percentage (95 to 100%) of low lead exposure (less than the standard of 0.01 mg/L) in drinking water samples in villages from several study provinces (Bi et al. 2010; Peng et al. 2008; Sun 2010).

Publication bias

A Begg’s funnel plot with the SE of SMD from each study plotted against its corresponding SMD did not show clear evidence of asymmetry, though two studies with a large SE also reported relatively large effect estimates, which may be consistent with publication bias or heterogeneity (Figure 3). The plot appears symmetrical for studies with larger SE, but with substantial variation in SMD among the more precise studies, consistent with the heterogeneity observed among the studies included in the analysis. Begg ($p = 0.22$) and Egger ($p = 0.11$) tests did not indicate significant ($p < 0.05$) departures from symmetry.

Pooled risk ratios

The relative risk of a low/marginal score on the CRT-RC test (<80) among children with high fluoride exposure compared to those with low exposure (16 studies total) was 1.93 (95% CI:
1.46, 2.55; $I^2$ 58.5%). When the model was restricted to 9 studies that used the CRT-RC and included only drinking water fluoride exposure (Chen et al. 1991; Fan et al. 2007; Li et al. 1995; Li et al. 2003; Li et al. 2010; Lu et al. 2000; Wang et al. 2006; Yao et al. 1996, 1997), the estimate was similar (RR 1.75; 95% CI: 1.16, 2.65; $I^2$ 70.6%). Although fluoride exposure showed inverse associations with test scores, the available exposure information did not allow a formal dose-response analysis. However, dose-related differences in test scores occurred at a wide range of water-fluoride concentrations.

Discussion

Findings from our meta-analyses of 27 studies published over 22 years suggest an inverse association between high fluoride exposure and children’s intelligence. Children who lived in areas with high fluoride exposure had lower IQ scores than those who lived in low exposure or control areas. Our findings are consistent with an earlier review (Tang et al. 2008), although ours more systematically addressed study selection and exclusion information, and more comprehensive in 1) including nine additional studies, 2) performing meta-regression to estimate the contribution of study characteristics as sources of heterogeneity, and 3) estimating pooled risk ratios for the association between fluoride exposure and a low/marginal Raven’s test score.

As noted by the NRC committee (NRC 2006), assessments of fluoride safety have relied on incomplete information on potential risks. In regard to developmental neurotoxicity, much information has in fact been published, although mainly as short reports in Chinese that have not been available to most expert committees. We carried out an extensive review that includes epidemiological studies carried out in China. While most reports were fairly brief and complete information on covariates was not available, the results tended to support the potential for
fluoride-mediated developmental neurotoxicity at relatively high levels of exposure in some studies. We did not find conclusive evidence of publication bias, though there was substantial heterogeneity among studies. Drinking-water may contain other neurotoxicants, such as arsenic, but exclusion of studies including arsenic and iodine as co-exposures in a sensitivity analysis resulted in a lower estimate, although the difference was not significant. The exposed groups had access to drinking-water with fluoride concentrations up to 11.5 mg/L (Wang et al. 2007), thus in many cases concentrations were above the levels of 0.7-1.2 mg/L (HHS) and 4.0 mg/L (US EPA) considered acceptable in the US. A recent cross-sectional study based on individual-level measure of exposures suggested that low levels of water fluoride (range 0.24 to 2.84 mg/L) had significant negative associations with child’s intelligence (Ding et al. 2011). This study was not included in our meta-analysis, which focused only on studies with exposed and reference groups, thereby precluding estimation of dose-related effects.

The results suggest that fluoride may be a developmental neurotoxicant that affects brain development at exposures much below those that can cause toxicity in adults (Grandjean 1982). For neurotoxicants, such as lead and methylmercury, adverse effects are associated with blood concentrations as low as 10 nmol/L. Serum-fluoride concentrations associated with high intakes from drinking-water may exceed 1 mg/L, or 50 μmol/L, thus more than 1000-times the levels of some other neurotoxicants that cause neurodevelopmental damage. Supporting the plausibility of our findings, rats exposed to 1 ppm (50 μmol/L) of water-fluoride for one year showed morphological alterations in the brain and increased levels of aluminum in brain tissue compared with controls (Varner et al. 1998).

The estimated decrease in average IQ associated with fluoride exposure based on our analysis may seem small and may be within the measurement error of IQ testing. However, as
research on other neurotoxicants has shown, a shift to the left of IQ distributions in a population will have substantial impacts, especially among those in the high and low ranges of the IQ distribution (Bellinger 2007).

The present study cannot be used to derive an exposure limit, as the actual exposures of the individual children are not known. Misclassification of children in both high- and low-exposure groups may have occurred if the children were drinking water from other sources (e.g., at school or in the field).

The published reports clearly represent independent studies and are not the result of duplicate publication of the same studies (we removed two duplicates). Several studies (Hong et al. 2001; Lin et al. 1991; Wang et al. 2001; Wang et al. 2007; Xiang et al. 2003; Zhao et al. 1996) report other exposures, such as iodine, and arsenic, a neurotoxicant, but our sensitivity analyses showed similar associations between high fluoride exposure and the outcomes even after these studies were excluded. Large tracts of China have superficial fluoride-rich minerals with little, if any, likelihood of contamination by other neurotoxicants that would be associated with fluoride concentrations in drinking water. From the geographical distribution of the studies, it seems unlikely that fluoride-attributed neurotoxicity could be due to other water contaminants.

Still, each of the articles reviewed had deficiencies, in some cases rather serious, which limit the conclusions that can be drawn. However, most deficiencies relate to the reporting, where key information was missing. The fact that some aspects of the study were not reported limits the extent to which the available reports allow a firm conclusion. Some methodological limitations were also noted. Most studies were cross-sectional, but this study design would seem appropriate in a stable population where water supplies and fluoride concentrations have remained unchanged for many years. The current water-fluoride level likely also reflects past
developmental exposures. In regard to the outcomes, the inverse association persisted between studies using different intelligence tests, although most studies did not report age adjustment of the cognitive test scores.

Fluoride has received much attention in China, where widespread dental fluorosis indicates the prevalence of high exposures. In 2008, the Ministry of Health reported that fluorosis was found in 28 provinces with 92 million residents (China News, 2008). Although microbiologically safe, water supplies from small springs or mountain sources created pockets of increased exposures near or within areas of low exposures, thus representing exposure settings close to the ideal, as only the fluoride exposure would differ between nearby neighborhoods. Chinese researchers took advantage of this fact and published their findings, though mainly in Chinese journals, and according to the standards of science at the time. This research dates back to the 1980s, but has not been widely cited at least in part because of limited access to Chinese journals.

In its review of fluoride, the US National Research Council (NRC 2006) emphasized that both the beneficial effects of fluoride on dental health and its adverse effects were incompletely documented. Our comprehensive review substantially extends the scope of research available for evaluation and analysis. Although the studies were generally of insufficient quality, the consistency of their findings adds support to existing evidence of fluoride-associated cognitive deficits, and suggests that potential developmental neurotoxicity of fluoride should be a high research priority. While reports from WHO and national agencies have generally focused on beneficial effects (CDC 1999; Petersen and Lennon 2004), the NRC report emphasized the need to consider potential adverse effects as well as benefits of fluoride exposure (NRC 2006).
In conclusion, our results support the possibility of adverse effects of fluoride exposures on children’s neurodevelopment. Future research should formally evaluate dose-response relations based on individual-level measures of exposure over time, including more precise prenatal exposure assessment and more extensive standardized measures of neurobehavioral performance, in addition to improving assessment and control of potential confounders.
References


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EMBASE (Elsevier B.V., Amsterdam, the Netherlands; http://www.embase.com) [accessed 10 April 2011].


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<td>347</td>
<td>329</td>
<td>7-10</td>
<td>Drinking water</td>
<td>2.47±0.75mg/L (high)</td>
<td>CRT-RC</td>
<td>No significant difference in IQ scores between children in the exposed and reference groups</td>
</tr>
<tr>
<td>Poureslami et al. 2011</td>
<td>Iran</td>
<td>59</td>
<td>60</td>
<td>6-9</td>
<td>Drinking Water</td>
<td>2.38 mg/L (high) 0.41 mg/L (reference)</td>
<td>Raven</td>
<td>Children in the high fluoride group scored significantly lower than those in reference group</td>
</tr>
</tbody>
</table>

*CRT-RC denotes Chinese Standardized Raven Test, rural version (Wang et al. 1989)*
### Table 2. Sensitivity analyses of pooled random-effect standardized weighted mean difference (SMD) estimates of child’s intelligence score with high exposure of fluoride

<table>
<thead>
<tr>
<th>Model</th>
<th>Available studies for analysis</th>
<th>SMD (95% CI)</th>
<th>I²</th>
<th>p-value test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Exclude non-standardized tests&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>-0.44 (-0.54, -0.33)</td>
<td>77.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2. Exclude non CRT-RC Tests&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
<td>-0.36 (-0.48, -0.25)</td>
<td>77.8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3. Exclude studies with other exposures (Iodine, Arsenic)&lt;sup&gt;c&lt;/sup&gt; or non-drinking water fluoride exposure&lt;sup&gt;d&lt;/sup&gt;</td>
<td>9</td>
<td>-0.29 (-0.44, -0.14)</td>
<td>81.8%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mental work capacity (Li et al. 1994); Japan IQ (Sun et al. 1991; Zhang et al. 1998); Chinese comparative scale of intelligence test (Yang et al. 1994)

<sup>b</sup>Weschler intelligence test (An et al. 1992; Ren et al. 1989; Wang et al. 1996); Chinese Binet IQ (Guo et al. 1991); Raven (Poureslami et al. 2011; Seraj et al. 2006); Binet-Siman (Xu et al. 1994)

<sup>c</sup>Iodine (Hong et al. 2001; Lin et al. 1991; Wang et al. 2001); Arsenic (Wang et al. 2007; Xiang et al. 2003; Zhao et al. 1996; Zhang et al. 1998 - already excluded, see footnote 1)

<sup>d</sup>Fluoride from coal-burning (Li et al. 2009; Guo et al. 1991; Li et al 1994 (already excluded, see footnotes a and b)
Figure Legend

Figure 1. Flow diagram of the meta-analysis

Figure 2. Random-effect standardized weighted mean difference (SMD) estimates and 95% CIs of child’s intelligence score associated with high exposure to fluoride. SMs for individual studies are shown as solid diamonds (♦), and the pooled SMD is shown as a non-filled diamond (◊). Horizontal lines represent 95% CIs for the study-specific SMDs.

Figure 3. Begg’s funnel plot showing individual studies included in the analysis according to random-effect standardized weighted mean difference (SMD) estimates (x-axis) and the standard error (se) of each study-specific SMD (y-axis). The solid vertical line indicates the pooled SMD estimate for all studies combined and the dashed lines indicated pseudo 95% confidence limits around the pooled SMD estimate.
Total abstracts identified from literature search (N=39)

- Duplicate records removed (N=2)
- Studies excluded because they did not meet inclusion criteria (N=3)

Studies for retrieval of detailed information (N=34)

- Studies with missing information on outcomes (N=6)
- Studies excluded due to questionably small standard deviations (N=1)

Studies included in meta-analysis (N=27)
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ren et al. 1989</td>
<td>Shandong</td>
<td>-0.75 (-0.97, -0.52)</td>
<td>4.22</td>
</tr>
<tr>
<td>Chen et al. 1991</td>
<td>Shanxi</td>
<td>-0.26 (-0.41, -0.10)</td>
<td>4.66</td>
</tr>
<tr>
<td>Guo et al. 1991</td>
<td>Hunan</td>
<td>-0.44 (-0.80, -0.08)</td>
<td>3.26</td>
</tr>
<tr>
<td>Lin et al. 1991</td>
<td>Xinjiang</td>
<td>-0.64 (-1.01, -0.28)</td>
<td>3.23</td>
</tr>
<tr>
<td>Sun et al. 1991</td>
<td>Guizhou</td>
<td>-0.95 (-1.16, -0.75)</td>
<td>4.36</td>
</tr>
<tr>
<td>An et al. 1992</td>
<td>I Mongolia</td>
<td>-0.57 (-0.83, -0.31)</td>
<td>3.98</td>
</tr>
<tr>
<td>Li et al. 1994</td>
<td>Sichuan</td>
<td>-0.40 (-0.74, -0.06)</td>
<td>3.39</td>
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<tr>
<td>Xu et al. 1994</td>
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<td>-0.93 (-1.35, -0.52)</td>
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<tr>
<td>Yang et al. 1994</td>
<td>Shandong</td>
<td>-0.50 (-1.01, 0.02)</td>
<td>2.36</td>
</tr>
<tr>
<td>Li et al. 1995</td>
<td>Guizhou</td>
<td>-0.55 (-0.70, -0.39)</td>
<td>4.68</td>
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<tr>
<td>Wang et al. 1996</td>
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<td>-0.38 (-0.65, -0.10)</td>
<td>3.88</td>
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<tr>
<td>Yao et al. 1996</td>
<td>Liaoning</td>
<td>-0.34 (-0.51, -0.17)</td>
<td>4.57</td>
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<tr>
<td>Zhao et al. 1996</td>
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<td>-0.54 (-0.76, -0.31)</td>
<td>4.22</td>
</tr>
<tr>
<td>Yao et al. 1997</td>
<td>Liaoning</td>
<td>-0.43 (-0.61, -0.25)</td>
<td>4.49</td>
</tr>
<tr>
<td>Zhang et al. 1998</td>
<td>Xinjiang</td>
<td>-0.17 (-0.55, 0.22)</td>
<td>3.09</td>
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<tr>
<td>Lu et al. 2000</td>
<td>Tianjin</td>
<td>-0.62 (-0.98, -0.25)</td>
<td>3.20</td>
</tr>
<tr>
<td>Hong et al. 2001</td>
<td>Shandong</td>
<td>-0.44 (-0.85, -0.03)</td>
<td>2.94</td>
</tr>
<tr>
<td>Wang et al. 2001</td>
<td>Shandong</td>
<td>-0.50 (-1.01, 0.02)</td>
<td>2.36</td>
</tr>
<tr>
<td>Li et al. 2003</td>
<td>I Mongolia</td>
<td>-0.10 (-0.25, 0.04)</td>
<td>4.71</td>
</tr>
<tr>
<td>Xiang et al. 2003</td>
<td>Jiangsu</td>
<td>-0.64 (-0.82, -0.46)</td>
<td>4.52</td>
</tr>
<tr>
<td>Seraj et al. 2006</td>
<td>Tehran</td>
<td>-0.89 (-1.28, -0.50)</td>
<td>3.08</td>
</tr>
<tr>
<td>Wang et al. 2006</td>
<td>Shanxi</td>
<td>-0.27 (-0.47, -0.06)</td>
<td>4.34</td>
</tr>
<tr>
<td>Fan et al. 2007</td>
<td>Shaanxi</td>
<td>-0.17 (-0.61, 0.27)</td>
<td>2.75</td>
</tr>
<tr>
<td>Wang et al. 2007</td>
<td>Shanxi</td>
<td>-0.26 (-0.44, -0.07)</td>
<td>4.46</td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>Hunan</td>
<td>-0.43 (-0.94, 0.08)</td>
<td>2.38</td>
</tr>
<tr>
<td>Li et al. 2010</td>
<td>Henan</td>
<td>0.07 (-0.08, 0.22)</td>
<td>4.69</td>
</tr>
<tr>
<td>Poureslami et al. 2011</td>
<td>Iran</td>
<td>-0.41 (-0.77, -0.04)</td>
<td>3.25</td>
</tr>
<tr>
<td>Overall (I-squared = 80.0%, p = 0.000)</td>
<td></td>
<td>-0.45 (-0.56, -0.34)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Dr Kathleen Theissen on NRC Review.

Endorsed by Dr Hardy Limeback

The NRC committee put together a very thorough evaluation of fluoride exposure in the US, much of which would be applicable also for NZ.

The NRC committee said, unanimously, that 4 ppm (4 mg/L) of fluoride is not protective of human health and should be lowered. We did not attempt to provide a recommendation for what a safe level would be. To allow anything resembling a margin of safety, various unofficial estimates of a suitable new standard range from 0-0.4 ppm, depending on several considerations, including how best to handle the question of carcinogenicity. The NRC committee did not, in any way shape or form, conclude that fluoridation is beneficial or safe.

We did look at several issues that pertain just to fluoridated water, primarily the concerns about silicofluoride usage. There is too much that is not known about the chemistry (water chemistry as well as biochemistry) of silicofluorides to say that they are safe for indiscriminate administration through the water supply.

For some endpoints [showing harm], many or most of the studies already involve fluoridated water [at 0.7 – 1 ppm] (osteosarcoma, Down syndrome, bone fracture).

Although promoters insist that dental fluorosis is not adverse or a health effect, the NRC reviewed at least 8 papers reporting an association between dental fluorosis and an increased risk of several adverse effects.”
Scientific knowledge in controversy: the social dynamics of the fluoridation debate

Brian Martin

with a commentary by Edward Groth III

Published in 1991 by State University of New York Press, Albany

The version here differs from the published version in a number of details of expression, a different format, different page numbering (151 instead of 274 pages) and omission of the index.

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Albert Burgstahler, Edith Waldbott, and many others (too numerous to mention) plied me with valuable information through correspondence. Gay Antonopoulos obtained copies of many publications for me through interlibrary loans. I thank the individuals listed in chapter 3 for their generosity in being interviewed. Discussions with Mark Diesendorf and Evelleen Richards provided me with insights. I received a large number of valuable corrections and comments on the earlier drafts from Albert Burgstahler, Brian Burt, John Colquhoun, Mark Diesendorf, Edward Groth III, Michael A. Lennon, Pam Scott, John Small, Donald Taves, and several anonymous reviewers. I especially thank Edward Groth III for his mammoth correspondence and for writing the commentary.
The 1 August 1988 issue of Chemical & Engineering News contained an article that caused a sensation in the long-running controversy over fluoridation. “Fluoridation of Water,” a special report written by associate editor Bette Hileman, surveyed the arguments both for and against the measure.

Fluoridation is the addition of the element fluorine — called “fluoride” when in an ionized form — to public water supplies as a measure to help prevent tooth decay in children. Hileman’s article outlined the standard view that fluoridation greatly reduces tooth decay, but also presented criticisms of this view. It described evidence both for and against claims that fluoridation may be involved in health problems, such as kidney disease, hypersensitive reactions, and cancer. It also recounted some of the methods used in the ardent promotion of fluoridation.

Hileman had not been involved in the fluoridation debate that has raged for decades. In writing the article, she studied the issue and consulted both supporters and opponents of fluoridation.

The ideas in her article were not new, and most of the evidence had been canvassed repeatedly in other forums. Why, then, did it cause such an impact? The reason is that never before had such a major scientific publication presented both sides to the debate in such an extensive treatment. In particular, never before in recent decades had a major professional association, such as the American Chemical Society, publisher of Chemical & Engineering News, given the scientific criticisms of fluoridation such credibility.

In the English-speaking countries at least, fluoridation has long been virtually untouchable for “serious scientists.” Opponents of fluoridation have been categorized as cranks, usually right-wing, and akin to those who think the earth is flat. In most dental, medical, and scientific journals, the arguments against fluoridation are given little space and little credence.

The Chemical & Engineering News article represented a dramatic contrast to the usual dismissal of antifluoridation views. The article generated news stories around the country and overseas, and led to a large volume of correspondence in later issues. Not surprisingly, opponents of fluoridation were delighted with the article; supporters were dismayed. More significantly, many correspondents congratulated Bette Hileman and Chemical & Engineering News for raising both sides of the issue for public discussion.

A BRIEF HISTORY

The use of fluoride to prevent tooth decay was promoted by various individuals in Europe in the 1800s. But the key events on the road to fluoridation occurred later and in the United States.

Frederick McKay, a dentist, first noticed staining of teeth in his Colorado patients in 1901. The colors ranged from white, yellow, and brown to black. In serious cases, there was also pitting of the enamel. Unlike most others who had noticed this mottling, McKay was intrigued by it and, over the next three decades, he pursued its origins. He noticed that, whereas people who had lived in a particular community from birth had stained teeth, newcomers to the district did not. Further investigation convinced McKay that water supplies were responsible.

It was not until 1931 that chemical analysis provided an answer to what was causing the discoloration: fluoride. H. V. Churchill, chief chemist at the Aluminum Company of America, supervised tests on water samples and, with McKay’s help, established a connection between fluoride in drinking water and mottled teeth. At about the same time, researchers M. C. Smith, E. M. Lantz, and H.
V. Smith in Arizona were able to produce mottling in the teeth of rats by feeding them fluoride. Also in the same year, H. Velu reported the fluoride-mottling link based on work in Morocco and Tunisia.

McKay had long observed that mottled teeth, although unsightly, seemed to be more resistant to decay. Discovery of the fluoride connection finally stimulated the United States Public Health Service (USPHS) to investigate the issue. Led by H. Trendley Dean, USPHS scientists (mainly dentists) carried out surveys of decay in towns with different fluoride levels and also carried out experiments with animals.

A range of levels of fluoride led to the severe mottling observed by McKay and others. Severe mottling was widespread at five parts per million (ppm) and above, but less common at lower concentration. Investigators looked to see whether there was a concentration that avoided most mottling while providing the benefits of reduced tooth decay. The level judged to be optimal in this regard was 1.0 ppm.

Only a small fraction of water supplies have high levels of fluoride naturally. Most have less than 0.2 ppm, a concentration too small to provide much impact on decay. In 1939, it was first proposed to add fluoride to waters that naturally have low fluoride levels. Fluoride would be added to bring the concentration to about 1.0 ppm.

The proposal struck a chord with a small number of dentists and public health officials in the United States who began campaigning vigorously for fluoridation. Many others were more cautious, including national health administrators and USPHS scientists who were still studying the dental effects of fluoride. In 1945, the first of a number of trials was begun. In these studies, two cities with similar characteristics were selected. Both had low natural levels of fluoride in the water. One city had fluoride added to its water supply, while the other’s water remained unfluoridated. Rates of tooth decay in the cities were monitored by periodic examination of children’s teeth.

The first study involved Grand Rapids, Michigan, where water was fluoridated in 1945. The water supply in control city, Muskegon, also in Michigan, remained unfluoridated. In the same year and in New York State, Newburgh’s water was fluoridated, while Kingston served as the control. Other important early studies involved fluoridation of the water supplies in Evanston, Illinois, and Brantford, Ontario. Oak Park, Illinois, and Sarnia, Ontario, served as the respective controls.

At the time, it was thought that fluoride acted by being incorporated into the growing enamel of children’s teeth. Hence, it would take quite a few years to see the full effect of fluoridation. The trials were planned to last ten or fifteen years. But after only a few years, the reported reductions in tooth decay were quite striking.

The proponents of fluoridation — in particular, a few enthusiastic advocates such as Wisconsin dentist John G. Frisch and Wisconsin dental administrator Francis Bull — were impatient with delay. Their lobbying was aimed especially at administrators in the USPHS, the most influential body in the public health field. H. Trendley Dean, whose work helped lay the ground for fluoridation, was not a supporter of rapid implementation, preferring to wait for the full results of the fluoridation trials. Along with others, his view was influential in maintaining the USPHS’s cautious stand throughout the 1940s.

The high-pressure tactics of Frisch, Bull, and others eventually won out. The top administrators of the USPHS apparently overruled Dean, and, in 1950, the USPHS endorsed fluoridation. Shortly afterward, two key professional bodies — the American Dental Association (ADA) and the American Medical Association (AMA) — also expressed support.

In the United States, however, decisions concerning public water supplies are made at the level of states, cities, or towns. The USPHS endorsement did not force any community to fluoridate, but it did provide vital authoritative backing for local individuals and groups that pushed for it.

The endorsements by the USPHS, ADA, and AMA were based on the claim that
fluoridation resulted in massive reductions in tooth decay, typically quoted as 50 to 60 percent, with no associated health risks, and at little cost to the community. At the time, dental decay was widespread, and many dentists felt unable to cope with it. Many people had all their teeth removed at an early age due to decay. In this environment, fluoridation was an attractive proposition. During the 1950s, a large number of communities moved to fluoridate their waters.

But almost as soon as the push for fluoridation began in the 1940s, a vocal and persistent opposition arose. In many communities where fluoridation was proposed, there were local individuals and groups that claimed that it was dangerous. The opponents typically claimed that it caused certain health problems in some people, and that it was “compulsory mass medication” and, therefore, unethical as well as an abuse of government power.

This basic configuration of proponents and opponents has persisted from the 1940s until today. The arguments on each side have remained essentially the same. The proponents assert that fluoridation massively reduces tooth decay rates, has no proven adverse consequences for health (except negligible mottling of teeth, which is only of cosmetic concern), and is the cheapest and most effective way of getting fluoride to all members of the population. The opponents say that the benefits are overrated, that there are a variety of proven or possible adverse health consequences (including skeletal fluorosis, intolerance reactions, and cancer), and that fluoridation is unethical because it is compulsory medication with an uncontrolled individual dosage.

Although the arguments have remained much the same, the fortunes of fluoridation have waxed and waned. The population drinking fluoridated water in the United States greatly expanded during the 1950s, but the opposition caused local reverses and stopped many proposals. Since the 1960s, the fraction of the U.S. population served by water supplies with added fluoride has increased only gradually, and now hovers at about one half. From the United States, the message about fluoridation was sent around the industrialized world. Dental and medical authorities, after investigation, usually endorsed the measure. In several countries — especially Australia, Canada, Ireland, and New Zealand — the pattern has been similar to that of the United States: there has been widespread adoption of fluoridation in the face of strenuous opposition. On the other hand, in Britain, only one in ten people drinks fluoridated water. In continental Western Europe, the measure was greeted even more cautiously by government bodies, and fluoridation is found in only a few localities. Only in the Netherlands did a sizable fraction of the population ever receive fluoridated water, and that program was terminated in the 1970s. By contrast, several Eastern European governments have introduced fluoridation on a more substantial scale, although it is far from universal.

In nonindustrialized societies, fluoridation is not usually a feasible proposition. In some countries, tooth decay was not much of a problem as long as the diet remained sufficiently traditional. But as the diet became Westernized, with large amounts of refined and sugary foods, tooth decay became a serious problem. The main obstacle to fluoridation in nonindustrialized countries is a lack of centralized public water supplies. Often, water is obtained from private wells not suitable for fluoridation.
Table 1 Percentage of the population served by water supplies with added fluoride, in selected countries in the late 1980s. For details see the appendix.

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
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<td>Australia</td>
<td>66</td>
</tr>
<tr>
<td>Austria</td>
<td>0*</td>
</tr>
<tr>
<td>Belgium</td>
<td>0</td>
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<td>Canada</td>
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</tr>
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<td>Finland</td>
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<td>France</td>
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</tr>
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<td>49</td>
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<td>Zimbabwe</td>
<td>0</td>
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</tbody>
</table>

* Greater than zero but less than 0.5 percent.

The proponent case has had no dramatic developments since 1950. The early promoters of fluoridation — including prominent figures such as H. Trendley Dean, John G. Frisch, and Francis Bull — have been followed by many others, such as Frank J. McClure, Ernest Newbrun, Herschel S. Horowitz, and Brian Burt. Other countries have their own lists of prominent proponents, including Douglas Jackson, John J. Murray, and Andrew J. Rugg-Gunn in Britain, and Noel Martin, Lloyd Carr, and Graham Craig in Australia.

The proponents refer to an accumulating body of data supporting the efficacy of fluoride in preventing tooth decay. They have also produced critiques on claims of hazards.

Compared to the proponents, it is easier to single out scientist opponents around the world. George Waldbott was undoubtedly the most prestigious opponent in the United States from the 1950s until his death in 1982. Others have been Frederick Exner, Albert Burgstahler, and John Lee. These critics have concentrated on the health hazards of fluoridation, including allergic and intolerance reactions.

In the mid 1970s, John Yiamouyiannis and Dean Burk joined the debate when they made dramatic claims about a link between fluoridation and cancer, and, since then, this issue has been a continuing and contentious one. Yiamouyiannis is the most prominent scientist opponent in the United States today. Another side to the opponents’ case is a critique of the evidence that fluoridation enormously reduces tooth decay. Waldbott, Exner, and others introduced this point, but the earliest comprehensive critique was presented by Philip Sutton, an Australian dental researcher, in 1959. In the 1980s, the critique of the size of benefits was taken up by John Colquhoun in New Zealand; Mark Diesendorf, Australia; John Yiamouyiannis, United States; and Rudolf Ziegelbecker, Austria. These individuals rank among the world’s leading scientist opponents of fluoridation.

The fluoridation debate has been such a bitter one that it is virtually impossible to say anything on the topic that cannot be questioned by one side or the other, or both.
This applies to the history of fluoridation as much as to anything else. The abbreviated account I have given is largely the picture as presented by the proponents of fluoridation. Some opponents have emphasized other events in the history, and given a different complexion to the whole account. I will have occasion to return to some events that have been the subject of debate. Suffice it to say that the selection of historical events as significant and the interpretation of motives are influenced by the stance of those making the selections and interpretations.

ANALYZING THE FLUORIDATION CONTROVERSY

The confrontation between expert proponents and opponents of fluoridation is a central focus in this book. By contrast, most social scientists have treated fluoridation as scientifically beyond dispute and have ignored natural scientists who are opponents. These social scientists have focused on the popular opposition to fluoridation and tried to explain it by factors such as ignorance, political conservatism, alienation, and confusion. This approach exempts the scientific aspects of fluoridation from scrutiny. The resulting analyses of the controversy are one-sided, usually serving the proponents by implicitly denigrating the opponents.

To analyze the fluoridation controversy, I prefer to use instead what can be characterized as a power picture of science. Instead of treating science solely as a search for truth, science is analyzed like other social activities such as advertising or transportation. In this picture, science is something people do that serves some interests in society more than others, especially the interests of scientists themselves and other groups with money and power enough to fund research and apply results.

Power is involved in all aspects of the practice of science, even in the daily processes by which scientists make decisions about what is valid knowledge. What is counted as knowledge depends on getting agreement from other scientists, and this may involve funding, status, or persuasive ability.

Fluoridation is a good topic for examining the dynamics of science and power because the opposition, while far from entirely successful, has not been totally submerged. The profluoridationists have been largely successful in maintaining their views as dominant among key groups in English-speaking countries, and this helps reveal the processes by which orthodoxy is established and perpetuated. But this insight is made possible by the persistence of a minority opposition, which ensures that the exercise of power in science is, to some extent, brought out into the open.

Furthermore, the issue has been a public one, and this means that many of the arguments for and against fluoridation have been spelled out with exceptional clarity. Internal disputes within the scientific community about theories of chemical catalysis, for example, do not generate very much accessible material for analysis. Finally, fluoridation combines technical, political, and ethical dimensions in a potent mixture.

In using the power picture of science to analyze fluoridation, I employ a variety of concepts and approaches. One is the idea of a “resource” or “tool.” Various elements — including slogans, claims of scientific knowledge, publications (Hileman’s article, for example), professional prestige, authoritative endorsements, community organizations, governments, and the mass media — have been used as resources in the struggle over fluoridation.

Another important concept is interest. For example, scientists have an interest in obtaining publishable results, establishing a good reputation, and having a good job. Corporate executives have an interest in increasing sales and profits, and also in protecting their executive status and privileges.

The idea of “social structure” or “social institution” is also valuable. For example, capitalism is a way of organizing work based on private property and the purchase of labor power. This results in patterned sets of
relationships between people, such as the employer-employee relationship.

Rather than try to analyze fluoridation by using a single unified theoretical picture, I prefer to approach it at a series of different levels, using the concepts already mentioned where appropriate. I have selected parts of the controversy that highlight the interacting roles of knowledge and power.

Chapters 2 through 6 can be seen as a series of examinations of the fluoridation debate, each showing the exercise of power on a successively larger scale. Each chapter reveals a power dynamic that casts a different light on the preceding chapters.

In chapter 2, I examine the arguments raised by scientists who support or oppose fluoridation in relation to benefits, risks, individual rights, and decision making. This can be considered to be an analysis at the level of intellectual debate, although, even here, the role played by other factors can be observed. In detailing the arguments, chapter 2 also sets the stage for the later analysis.

Proponents and opponents line up in an almost completely predictable fashion on the entire range of arguments, from science to ethics. Chapter 3 probes this remarkable coherency of viewpoints, which can be explained as a product of the polarizing nature of the fluoridation debate itself: the partisans develop their coherent views in order to make a solid case in the rough and tumble of public debates and campaigns. This analysis at the level of social psychology suggests that the scientific arguments outlined in chapter 2 have been shaped, directly or indirectly, by the requirements of public fluoridation debates.

Chapter 4 turns to the struggle for credibility, which involves obtaining authoritative backing and attacking the credibility of those on the other side. This means going far beyond attacking the credibility of scientific statements, which would constitute part of an intellectual dispute. Rather, the attack is on the credibility of individuals as scientists and as honest, sensible, and upstanding citizens. This is a level involving every possible use of rhetoric against the reputations of individuals as a tool in a struggle for authority. The existence of systematic attempts to undermine the credibility of individuals as people — rather than the credibility of their arguments, and to gain support on the basis of authority — shows the limitations of dealing only with arguments and views as in chapters 2 and 3.

Another exercise of power has been control over publication, research funding, and professional accreditation. In all these areas there are examples of the overt use of the power of the dental profession against antifluoridationists. Chapter 5 examines this side of the controversy by placing it in the context of the dental profession’s support for fluoridation. This analysis at the level of professional power shows that the debate over scientific knowledge about fluoridation has involved more than language. It is not solely an intellectual dispute, nor a verbal duel for authority and credibility, as treated in chapters 2 to 4. Rather, the material basis for scientific communication, scientific research, and professional advancement — namely, publications, research grants, and accreditation — have been used as tools in the struggle.

Moving beyond a focus on individual researchers and partisans, chapter 6 looks at the role of industrial corporations whose interests may have shaped the context of the fluoridation debate. This analysis, at the level of corporate power, suggests that the issue of fluoridation might not have arisen in the form that it took — or even become an issue at all — had the historical configuration of corporate interests and the dental profession been different.

Proceeding through chapters 2 to 6, the focus changes from the exercise of power at the level of individuals and arguments to the role of power at the large scale of social structures. All levels are required for a full picture. The large-scale, structural perspectives provide the context for detailed disputation; without these wider contexts, the debate might be imagined to be proceeding on the basis of fact and logic alone. But the structural perspectives do not tell the story by themselves. Rather, they provide a framework for and an influence on debate. Even so, only a
detailed examination can tell what arguments are actually developed and deployed.

In chapter 7, I attempt to draw out some implications of the analysis. How should the debate be resolved? Can the debate be resolved? In retrospect, how could the proponents and the opponents have improved their strategies? I conclude that there is no simple answer to any of these questions. In confronting the fluoridation debate, one also confronts — implicitly or explicitly — basic issues about the organization of society.

A basic theme in my analysis is that it is impossible to separate the scientific and power dimensions of the fluoridation issue. In order to assess the scientific work on fluoridation, it is necessary to understand the wider social context — the careers of key individuals, the commitment of the USPHS and the ADA, and the potential of corporate support or hostility. All of these can influence what scientific research is done or not done, the predisposition of researchers to obtain particular types of results, and the assessment of contrary findings. The body of research relating to fluoridation and the common evaluations made of it cannot be separated from the wider power dimensions of the controversy.

Conversely, it is impossible to understand fully the power dimensions of the controversy without assessing the scientific issues. The common view that fluoridation is scientifically beyond question, as well as the minority view that it is scientifically indefensible, eliminate the possibility of understanding how scientific knowledge claims are embedded in power struggles. Assessing the struggles over scientific knowledge is essential to a full understanding of wider power dimensions.

It is not my task in this analysis to either support or oppose fluoridation. So far as I am concerned, that is a side issue. My interest is in the analysis of scientific knowledge as it is used and shaped in the course of a bitter public dispute. In developing my analysis, I have benefitted greatly from a handful of writers who have analyzed the issue without assuming that fluoridation is scientifically correct.11

Chapter 8 deals with the social analysis of the fluoridation controversy. I briefly describe standard approaches in previous studies, contrast my own approach with them, and defend my formal agnosticism about fluoridation. I also recount a potential difficulty encountered by those studying contemporary controversies: the involvement of the researcher, reluctant or otherwise, directly in the controversy.

In this book I present one way of looking at the issue of fluoridation. It is certainly not the only way. It is my hope that, in selecting some perspectives not often given attention previously, some will see this issue in a new light.

When I circulated the first draft of this book to a range of individuals for comment, I also invited them to write responses to my text. Edward Groth III took up this offer, and I am greatly pleased to have his insightful essay as part of this book. It deals with how to assess the scientific evidence on fluoridation. It is highly appropriate that Groth’s views should be represented here, since his pioneering work on the fluoridation controversy has received insufficient attention.12

NOTES


2. Stated in each issue of Chemical & Engineering News is the disclaimer that the American Chemical Society “assumes no responsibility for the statements and opinions advanced by the contributors to its publications.” Nevertheless, the views expressed are given considerable legitimacy by their very publication.

3. In a special issue of the Journal of the American Dental Association on fluoridation, the introduction likened antifluoridationists to those who opposed fire and the wheel, who believed the earth is flat, who opposed the automobile, who opposed anesthesia, and who opposed blood transfusions, vaccination, immunization, Pasteurization, and chlorination. “Fluoridation is Here to Stay,” Journal of


5. One part per million fluoride means one milligram of fluoride in each liter of water.


7. This figure understates the extent of fluoridation of public water supplies, because many of the 50 percent who drink unfluoridated water do not use public water supplies but instead obtain water from wells and other sources. Furthermore, some waters are naturally fluoridated and do not count as having added fluoride.

8. In referring to leading scientist supporters or opponents of fluoridation, I use the term scientist loosely to include doctors and dentists who are familiar with scientific research on fluoridation.


10. My approach to the fluoridation controversy is elaborated and placed in context in chapter 8.


12. Chapter 8 was written after Groth’s commentary was completed, hence my remarks in chapter 8 on his contribution. Groth gave me comments on a draft of chapter 8, but preferred to leave his own essay unaltered.
Arguments

The aim in fluoridation is to adjust the concentration of fluoride in public water supplies to the optimal level for dental health. The main beneficiaries are children up to the age of twelve or perhaps as old as sixteen. Benefits for adults are less certain.

The higher the concentration of fluoride in the water, the greater is the preventive effect against dental caries, commonly known as tooth decay. But as McKay discovered back in 1901, if the concentration is too high, staining and, in severe cases, pitting occurs. The optimal concentration of fluoride — considered to be about 1.0 parts per million (ppm) — prevents tooth decay as much as possible without causing much mottling. In hotter climates where people drink more water, the concentration of fluoride is set lower, perhaps to 0.7 ppm. In cooler climates where people drink less water, the concentration is set higher, such as 1.2 ppm.

Fluoridation is not intended to provide a controlled dosage but rather to mimic naturally fluoridated water supplies which, as shown by H. Trendley Dean’s studies in the 1930s, result in less tooth decay throughout the community. People who drink one liter of water with 1.0 ppm fluoride swallow exactly one milligram of fluoride. But different people drink different volumes of water. Some, such as laborers and athletes, may drink several liters per day. Others may drink only milk or fruit juice and obtain no fluoride from the water supply. So, whereas the concentration of fluoride in the water can be specified and controlled, the dosage of fluoride to any individual is uncontrolled.

The most obvious way to ensure a precise dosage of fluoride is to take a tablet. Fluoride tablets have been advocated and used widely, especially in regions where water is not fluoridated or where there is no public water supply. The biggest problem with fluoride tablets is that most people find it a chore to take them. Children are expected to take them daily for the first 12 or so years of their life, and experiments show that few parents are able to instill the required habit.

By comparison, it requires no will power to reap the benefits of water fluoridation. Simply by virtue of drinking water, most people will obtain fluoride. This means that individuals who never go to a dentist, or those who have decay-producing diets due to poverty, ignorance, or preference, still obtain the benefits of fluoride. Admittedly, some children obtain less than the amount of fluoride specified as optimal. But water fluoridation still provides a wider cross section of benefits than do fluoride tablets, since more people drink some water than would persist in taking tablets.

Most promoters of fluoride to prevent tooth decay prefer water fluoridation over other methods of obtaining fluoride — so much so that the word “fluoridation” is normally taken to mean addition of fluoride to public water supplies. Water fluoridation gets to a larger fraction of the public and is also thought to be more effective than other approaches. It is also quite inexpensive on a per-capita basis, even when one considers that large volumes of fluoridated water are used in industry, to water lawns, and for other purposes. Only a tiny fraction of the water supply is actually consumed.

**The Case for Fluoridation**

The strength of the arguments in favor of fluoridation rests on the widely experienced pain of tooth decay, plus the claim that decay will be dramatically reduced by fluoridation without any effort, harm, or much expense. A large segment of the population has experienced toothaches or seen their effects on family or friends. This set of experiences provides a powerful motivation to seek a way of reducing or eliminating this pain. Dentists
in particular witness the problem regularly and this helps explain why so many of them support fluoridation.

Fluoridation promises a solution that seems miraculous. Simply by adding a tiny concentration of a tasteless element to the water supply, tooth decay is supposed to be reduced by one-half or even more.

A limitation of the basic argument for fluoridation is that it only promises to prevent tooth decay. That doesn’t help someone with a toothache now. If a fluoride tablet could positively cure decay, it would be much easier to sell. A quick cure is something that can be observed by anybody (although the cause of the cure may be debatable). Prevention is altogether harder to document and, therefore, harder to sell.

In their arguments for fluoridation, proponents most commonly refer to numerous scientific studies. The classic trials in Grand Rapids and Muskegon, Michigan; Newburgh and Kingston, New York; and other communities were designed to compare populations drinking fluoridated water against those drinking unfluoridated water. The researchers found that decay rates were greatly reduced in the fluoridated communities.

For example, John J. Murray and Andrew J. Rugg-Gunn refer to these studies in their authoritative book Fluorides in Caries Prevention. They conclude, “the strength of the experimental proof of the caries-inhibitory property of fluoride drinking water lies … in the fact that the three American studies, carried out by different investigators in different parts of the country, reached similar conclusions: addition of 1 ppm fluoride in the drinking water reduced caries experience by approximately 50 per cent.” In surveying ninety-five studies from twenty countries on the effectiveness of fluoridation, Murray and Rugg-Gunn state that “The modal [most common] percentage caries reduction is 40-50 per cent for deciduous teeth and 50-60 per cent for permanent teeth — this is in agreement with the oft-quoted statement that ‘water fluoridation reduces dental decay by half.’”

In a briefer discussion of key clinical trials, prominent dental researcher Ernest Newbrun states that “the conclusion that fluoride is effective in reducing dental caries prevalence is based not only on clinical diagnosis of carious lesions but also on blind clinical and radiological examination of children and on strictly objective criteria such as missing permanent first molars.” Similarly, Wesley O. Young, David F. Striffler, and Brian A. Burt, in a dental textbook, state that “Fluoridation is the most effective and efficient means of reducing dental caries on a community-wide basis. It reduces caries prevalence by 50 to 60 percent in the permanent dentition among children born and reared in a fluoridated community.”

These types of scientific findings are easy to use for promotional purposes. The results are presented typically to dentists, doctors, politicians, and the general public in the form of statements such as “More than 50 years of research and practical experience have proved beyond a reasonable doubt that fluoridation is effective in preventing tooth decay. Hundreds of studies have demonstrated reductions in tooth decay of 60-70% in communities with either natural or controlled fluoridation.”

Many antifluoridationists have left unchallenged the research results showing reductions in tooth decay by fluoridation. There are several reasons for this. First, there are many studies showing such reductions, as well as numerous studies of the microscopic processes in the mouth that explain how reductions can occur. It is hard to counter such a preponderance of research. Second, most of those who have done research on the effect of fluoridation on tooth decay have been supporters of fluoridation. There have been few inside this group of researchers to take up the antifluoridation cause. Finally, the arguments about health risks and individual rights are much more powerful tools for opposing fluoridation.

**QUESTIONING THE BENEFITS**

Nevertheless, there have been some criticisms of the claims for large benefits from fluoridation. The first thorough critique was by Philip R. N. Sutton, then a senior research fellow at
the University of Melbourne Dental School. Sutton’s monograph, *Fluoridation: Errors and Omissions in Experimental Trials*, was published in 1959 by Melbourne University Press. Sutton examined the five classic fluoridation trials, of which the comparison between Grand Rapids and Muskegon was the first. He began by stating that these trials constituted “the main experimental evidence which has led to the introduction of this process [fluoridation] as a public health measure.”

Sutton’s work is a critique of the claims for massive benefits from fluoridation. He proceeds by scrutinizing the central research papers and exposing methodological flaws in them. For example, he points out the problem of examiner bias: if the dental examiners who count the number of decayed, missing, and filled teeth in children know whether a particular child is from the fluoridated or the unfluoridated community, this may unconsciously affect their evaluation. (Sutton points out elsewhere that assessment of whether a cavity is present depends on whether a dentist’s probe encounters hard or soft material in the tooth, a process involving a distinct evaluative element. Counting missing and filled teeth is a less contentious process.)

Sutton suggests that a proper blind procedure would involve bringing children from both fluoridated and unfluoridated communities to the examiners in such a way that they would not know which children were which. Because this was not done in any of the classic studies, they are all open to the criticism that examiners unconsciously found what they wanted or expected to find.

Sutton raises a large number of points in regard to the classic studies, including lack of sufficient baseline statistics prior to fluoridation, variations in sampling methods, examiner variability, and sampling error. In the Grand Rapids study, the results were limited by the fact that the control city, Muskegon, was fluoridated in 1951, six years after the beginning of the study.

The power of Sutton’s critique is that it exposes the “soft underbelly” of scientific research, namely that scientists do not do everything the way they are supposed to in theory. But this does not in itself automatically lead to the conclusion that fluoridation doesn’t work. A piece of research can come up with a valid conclusion even though the methods used are less than perfect.

Sutton himself did not carry out a proper controlled study of fluoridation. Nor did he prove that the studies he examined came to the wrong conclusion. He made a lesser claim: that the scientific methods used in the classic studies were inadequate, and, hence, these studies are not a good basis for proceeding with fluoridation. His assumption is that the onus of proof should lie with those promoting fluoridation to conclusively demonstrate its benefits.

After Sutton’s monograph was published, the president of the Australian Dental Association sent copies to the scientists who had been in charge of the classic studies. As a result, several reviews were published, mainly in the *Australian Dental Journal*. In the second edition of his monograph, published in 1960, Sutton included four reviews and his replies to them.

Several of the reviewers deal with technical points, either defending the studies against Sutton’s criticism or criticizing Sutton’s account. For example, Sutton had said that, in two of the control or unfluoridated cities, there were significant changes in tooth decay rates. This was contrary to the reports of the studies claiming that these rates had stayed about the same. R. M. Grainger takes this up in one of fifteen specific points in his review. He said the important thing was that, in the control cities, the changes noted by Sutton “were upward trends or mere fluctuations” compared to the fluoridated city of Brantford where the change was “a highly significant continual downward trend.” Replying to Grainger, Sutton notes that the chance that fluctuations would be as great as noted was 1 in 370 and therefore these changes were significant rather than “mere fluctuations.” Sutton also points out that the “highly significant continual downward trend” in decay rates in Brantford appeared only in children aged twelve to
fourteen, and therefore Grainger’s claim of a continual downward trend in Brantford is incorrect and misleading.\textsuperscript{10}

This example is one of the more readily understandable points of technical disagreement between Sutton and his critics. It illustrates the small details involved. This technical attack and counterattack can be interpreted as a battle for credibility, in which showing even tiny mistakes in the other side’s argument is important since it reflects on the soundness of their case.

If the first basic response to Sutton was to challenge him on technical points, the second response was to question whether his argument was relevant to fluoridation at all. Donald Galagan, the assistant chief of the Division of Dental Public Health, United States Public Health Service, made this point strongly. It is an important argument, used ever since by profluoridationists.

Galagan argues that the scientific basis of fluoridation had been solidly established \textit{before} any of the classic control studies. The benefits of fluoride were shown by examination of children who drank naturally fluoridated water. “The fact is that the projects at Brantford, Grand Rapids, Newburgh and Evanston were designed primarily to evaluate the technical, financial and administrative problems associated with the controlled addition of fluorides to a municipal water supply, and, secondarily, to \textit{demonstrate} the effectiveness of the procedure to the profession and the public.”\textsuperscript{11}

The basis of Sutton’s monograph was the claim that “proposals to fluoridate domestic water are almost entirely based” on the results of experimental trials in these four cities.\textsuperscript{12} Arguably, one reason why studies of naturally fluoridated communities cannot be used to draw ironclad conclusions about artificially fluoridated communities is that most waters that have high natural levels of fluoride also have high levels of other minerals such as calcium and magnesium, and also contain trace elements such as strontium and boron. It is difficult to rule out that the high mineral content of so-called hard water, which is usually associated with high natural fluoride levels, may contribute to the resistance of teeth to decay. The controlled studies were exactly the sort of test required to determine whether added fluoride alone, without the other elements, would reduce tooth decay.

Sutton’s reply to Galagan does not rely so much on this sort of logic (which was implicit in Sutton’s analysis) as on quotations from key researchers involved in the classic trials themselves. For example, he quotes one group of researchers involved in one of the two Brantford studies as saying in 1951, “It was recognized that fluorine in the public water supply was not a proven method for the prevention of dental caries, and that it might take ten years to prove or disprove its preventive value.”\textsuperscript{13} Through a series of quotations, Sutton attempts to show that, at the time, the controlled studies were seen as tests of the effectiveness of artificial fluoridation against tooth decay. In this way, Sutton asserts the relevance of his critique of methods used in those studies.

It is important to note that what is ostensibly a technical dispute about scientific experimentation actually involves a dispute about history: the history of fluoridation. Sutton interprets the history as one in which the controlled studies of matched communities were seen as a crucial test of the effectiveness of fluoridation. Many of the proponents of fluoridation interpret the history as one in which fluoridation was established scientifically in the 1930s through studies of naturally fluoridated communities and through animal studies, and in which the controlled studies of matched communities were demonstrations of the effectiveness of fluoridation.

A related response to Sutton is to point out that scientific understanding of the mechanism by which fluoride prevents tooth decay has changed. In the 1940s and 1950s, it was accepted that fluoride needed to be incorporated into the enamel of growing teeth. But in recent decades, the topical or surface effect of fluoride has been assessed to be of equal or greater significance. Fluoride in the saliva is thought to inhibit decay, for example, by promoting remineralization at the surface of the tooth. The classical studies and Sutton’s
critique do not allow for the topical effect of fluoride in drinking water, which could reduce tooth decay quickly.

Although Sutton’s criticisms were met with a vehement response in the reviews published in 1960, little debate on this topic was carried out thereafter. Sutton did not pursue his challenge, and antifluoridationists, while sometimes citing his views, did not take them up as a central plank in their campaigning. The intricate technical points involved are not the best type of material for public campaigning. For their part, the proponents have assumed that the effectiveness of fluoridation has been established. Few texts or review papers on fluoride and tooth decay even mention the existence of a critique by Sutton or anyone else.¹⁴

This situation changed only in the 1980s when John Colquhoun, Mark Diesendorf, and Rudolf Ziegelbecker published critiques of the effectiveness of fluoridation. Diesendorf’s approach is similar to Sutton’s. He examines studies claiming to show that fluoridation reduces tooth decay to determine whether they conform to a rigorous methodological ideal in which a control is used, baseline data are available, examinations of cavity rates are carried out in a blind fashion, and there are no confounding factors. Even though there have been dozens of studies — almost all of them showing a reduction in tooth decay associated with fluoridation — Diesendorf argues that few, if any, are satisfactory statistically.¹⁵

Diesendorf has injected two important points into the fluoridation debate. First, he quotes studies and data showing significant declines in tooth decay in unfluoridated regions. Second, he quotes studies and data showing continued declines in tooth decay in fluoridated regions, long after the maximum effects should have been obtained.

For example, seven-year-old children should obtain maximum benefits if their water supply has been fluoridated for seven years or more (although benefits may well occur in less than seven years). For a community fluoridated for twenty years, tooth decay rates for seven-year-olds should be stable for the last thirteen years, unless other factors are operat-
same token, the disadvantage of turning the issue into a very technical debate. Arguments about the significance of figures for decayed, missing, and filled teeth in twelve-year-olds in Newburgh or Sarnia in 1950 are hardly the sort of thing to excite the public or even galvanize dentists.

NEITHER NECESSARY NOR SUFFICIENT

Another approach used to criticize fluoridation is more accessible. The argument here is to say that fluoride is neither necessary nor sufficient for good teeth. The terms “necessary” and “sufficient” are used here as in formal logic. If fluoride is not necessary, that means that a person can have good teeth without fluoride. This is a counter to the claim by proponents that fluoride is a missing ingredient in human nutrition and that fluoridation is essentially the “topping up” of water supplies to what nature would normally supply as optimal.

Opponents argue that many people did — and still do — have excellent teeth although their drinking water contains almost no fluoride and although they obtain no extra fluoride through toothpaste or other nondietary sources. (There are traces of fluoride in most foods, so, in practice, a completely fluoride-free diet is virtually impossible.)

The new conventional wisdom is that fluoride has a greater effect in the mouth, at the surface of the teeth, than it does incorporated into the growing teeth as a result of swallowing it. As noted, this knowledge has been used by proponents to explain rapid improvements in decay rates in the trials of fluoridation. But it also provides a new argument for antifluoridationists.

Why drink fluoridated water? Why not just rinse out one’s mouth with fluoridated water, gaining most of the benefits, and then spit it out, avoiding most of the risks? This can be seen as a modification of the argument that fluoride is not necessary for good teeth. It accepts that fluoride may be helpful in the mouth but, to obtain most of the benefits, it is not necessary to swallow it.

The other part of the argument is that fluoridation is not sufficient to prevent tooth decay because some people have many cavities in spite of drinking fluoridated water.

The opponents’ argument is that tooth decay is not caused by a lack of fluoride, but rather by poor diet, in particular eating refined sugary foods. Those populations with excellent teeth in spite of little fluoride are ones whose diets are largely unprocessed and contain a preponderance of grains, fresh vegetables, and fruits. Those populations with many decayed teeth in spite of fluoridation typically eat highly processed foods containing considerable amounts of sugar. The brushing of teeth and practicing oral hygiene in general may also be relevant in this context.

Some opponents of fluoridation argue that it is better to address the ultimate cause of tooth decay, namely diet, with avoiding sugary foods as the main emphasis. They also point to the dietary role of other minerals besides fluoride in building strong teeth. These include calcium, of course, plus phosphorous, strontium, vanadium, and molybdenum. Poor diet can also have consequences for dental health by affecting the gums. Periodontal disease is a more serious problem than decay, especially in adults.

This means of criticizing fluoridation does not impress the proponents, especially dentists. Some of them have been pushing for better diet for many decades. Typically the proponents simply say something like this: “We agree that sugary foods are a primary cause of tooth decay. But, in spite of major campaigns, most people will not change their diets — they prefer processed and sugary foods. Diet is something we can influence only a little. But we can control fluoride levels in the water supply, and, in this way, do something definitive against tooth decay.”

When the debate goes in this direction, it is apparent that it is no longer strictly about fluoridation, but deals with preventive dentistry in the broadest sense. In this area, there is actually considerable agreement between the proponents and opponents of fluoridation: both support better diet. But this has never been a basis for establishing harmonious relations. The opponents in particular have emphasized criticism of
Arguments

Fluoridation rather than positive alternatives. For example, in The American Fluoridation Experiment, the most authoritative book critical of fluoridation published in the 1950s, only a few of the more than two hundred pages are devoted to criticism of the claims about benefits of fluoridation, and fewer still deal with alternatives.  

**HEALTH RISKS**

Overall, the debate about the existence and size of benefits from fluoridation has been a sideline to the main arena, the risks involved. The debate here is straightforward. The opponents claim that fluoridation causes serious health problems in a fraction of the population. The proponents deny the existence of any such problems.

The apparent simplicity of these issues is part of their attraction. Everyone can understand a statement that fluoridation causes poisoning or cancer, or the claim that fluoridation is entirely safe. Statistical nuances do not intrude so obviously. Yet, in practice, the debate about hazards involves just as many scientific complexities as the debate about benefits.

There are many claims made about the adverse effects of fluoridation on human health. I will concentrate only on effects considered to be the most important by prominent critics of fluoridation who are scientists, such as Albert Burgstahler, Dean Burk, Frederick Exner, John Lee, George Waldbott, and John Yiamouyiannis. Three key areas are chronic fluoride toxicity, intolerance reactions, and genetic effects. Because these and other topics have received exhaustive treatments, only a few examples will be used to illustrate the ways in which the debate has proceeded.

“Chronic fluoride toxicity” refers to toxic effects caused by a long period of exposure to low levels of fluoride. Many fluoride compounds are poisonous. For example, a dosage of several grams of sodium fluoride can cause death in human adults. The effects from large doses are called “acute effects.” Because fluoridation involves the ingestion of tiny amounts of fluoride over many years, it is the possible long-term or chronic effects that are of greatest concern.

Opponents refer to mottling of teeth as a sign of chronic toxicity. They consider that it reflects an excessive intake of fluoride that may also be affecting other organs or functions of the body. Proponents see mottling as only a cosmetic problem with no health implications. The different interpretations of mottling are representative of different approaches to the issue of toxicity. At least both sides agree that mottling does occur.

The only other consequence of fluoride on which there is much agreement is skeletal fluorosis, a bone disease caused by excessive fluoride intake that, in serious cases, can cause crippling deformities. It is agreed that skeletal fluorosis is found in some high-fluoride regions in India and several other countries, typically with 2.0 ppm to 10.0 ppm fluoride in the water. Occupational exposure to high levels of fluoride is also linked to skeletal fluorosis.

Opponents say that 1.0 ppm of fluoride in water can be enough to cause symptoms of skeletal fluorosis in some people. They point out that, in India and other countries with well-documented incidents of skeletal fluorosis, there are many more severe cases when the fluoride level in drinking water is very high at 5.0 to 10.0 ppm. But there are also some cases seen even at fluoride levels of 1.0 ppm or lower. Also of concern to opponents are subtle changes in the skeleton due to fluoride, which occur prior to the clinical symptoms of skeletal fluorosis.

Proponents say, to the contrary, that the margin between 1.0 ppm and the concentration required to cause skeletal fluorosis is sufficient. This divergence of opinion is possible because there have been very few reported cases of skeletal fluorosis in Western countries. Other factors, in addition to fluoride, may contribute to the high levels of skeletal fluorosis in some parts of India.

The opponents argue that the margin between the 1.0 ppm concentration used for fluoridation and the somewhat larger concentrations usually required to cause overt skeletal
fluorosis and other symptoms of chronic fluoride toxicity is simply not great enough. They consider that a small fraction of the population may be experiencing some forms of chronic fluoride toxicity.

The proponents argue that there is no evidence in Western countries that fluoridation contributes to skeletal fluorosis. As one report puts it, “In non-tropical countries there has been no report of clinically symptomatic skeletal fluorosis in areas with drinking water less than 4 mg/litre [4.0 ppm].”

“Non-tropical countries” eliminates the evidence from India. “Clinically symptomatic skeletal fluorosis” excludes toxic effects that do not show up as overt or clinical symptoms. The 4.0 ppm figure puts fluoridation’s 1.0 ppm in the safe range.

(Despite its qualifications, the foregoing statement can still be challenged. There are some reported cases of skeletal fluorosis in the United States and other “non-tropical countries” that contradict it. To be more accurate, the statement would have to exclude cases where other factors contribute to skeletal fluorosis, such as kidney failure and excessive thirst.)

Each side puts the onus of proof on the other. The proponents cite a scarcity of reports of “clinically symptomatic skeletal fluorosis” as a refutation of the danger. In other words, it is up to the opponents to come up with studies showing significant effects at water fluoridation’s level of 1.0 ppm. The opponents, on the other hand, claim that the margin of safety is too small, leaving it to the proponents to demonstrate that 1.0 ppm does not cause problems for at least some people.

This divergent interpretation of evidence reflects a theme in the debate that goes back to the original studies. What constitutes a sufficient examination of the health consequences of fluoridation? The proponents repeatedly assert that there is no evidence of risk from fluoride at the dosages involved with water fluoridation.

Newbrun summarizes some of the early investigations showing the safety of fluoridation. “Very thorough medical examinations of the children accompanied both the Newburgh–Kingston and the Grand Rapids–Muskegon fluoridation studies. No significant differences in health or in growth and development were found between children in study and control cities. The Newburgh examination was very detailed and included tonsillectomy rates, height and weight, onset of menstruation, bone density by X-ray examination of hands and knees, skeletal maturation, hemoglobin level, erythrocyte count, leukocyte count, urinalysis, and skin moisture, texture, color, and eruptions. The conclusion of this long-term pediatric study was that, aside from the reduction in caries, there was no indication of any systemic effects, adverse or otherwise, from the use of fluoridated water.”

A typical overall conclusion is that of Murray and Rugg-Gunn. “The effect of water fluoridation on general health has been thoroughly investigated in a series of population studies. There is no evidence that the consumption of water containing approximately 1 ppm F (in a temperate climate) is associated with any harmful effect.”

One way to challenge these findings is to demonstrate individuals who react adversely to fluoridation. If only a small fraction of individuals react this way, the effect may not readily show up in statistical studies of populations, especially if the adverse reaction can result from other causes as well as fluoride.

For many years, the leading U.S. scientist opponent of fluoridation was George L. Waldbott, an allergist and researcher who campaigned against the measure from the mid-1950s until his death in 1982. Waldbott published many articles in which he documented adverse reactions by particular individuals to fluoride, often in amounts associated with water fluoridation.

Supporters of fluoridation — with a few exceptions — have ignored or dismissed Waldbott’s findings. For example, H. C. Hodge in his “Evaluation of some objections to water fluoridation,” says “Reports of ‘fluoride allergy’ have come principally from the late Doctor George Waldbott.” After describing one of Waldbott’s cases, Hodge comments, “Competent immunologists do not
accept Waldbott’s case histories as evidence that fluoride allergy exists.”

Hodge then quotes the executive committee of the American Academy of Allergy, which stated, in 1971, “There is no evidence of allergy or intolerance to fluorides as used in fluoridation of community water supplies.”

Hodge does not refute Waldbott’s extensive evidence, but uses an argument from authority. Certainly the executive committee of the American Academy of Allergy provided no scientific refutation of Waldbott’s findings. Furthermore, Waldbott interpreted most of his cases in terms of intolerance reactions, not allergy as implied by Hodge.

At least Hodge did go to the trouble of briefly describing Waldbott’s findings. In Murray and Rugg-Gunn’s key book *Fluorides in Caries Prevention*, Waldbott’s studies are not mentioned at all. This is the more common pattern.

One of the arguments used against claims of fluoride toxicity in individuals is that studies must be double blind: that is, the reaction of the “subject” to drinking water or tablets should be investigated using an experimental procedure in which neither the investigator nor the subject knows which samples contain fluoride and which do not. This is important, since knowledge on the part of investigators or subjects could result in false responses. An example would be if subjects reacted physically simply on being told they had ingested fluoride. If the subject reacts to a placebo (no fluoride), this shows the lack of a physical basis for the reaction.

Many of Waldbott’s patients who showed reactions to fluoride were not tested in blind conditions. This allows critics to be skeptical. But some of his patients were tested in blind conditions.

Some of Waldbott’s critics also suggest that his claims have not received independent verification. Admittedly, Waldbott did not allow outsiders access to his files on his patients, making it impossible for his unpublished documentation to be inspected or his patients to be tested by other doctors. But there have been quite a number of other blind and double-blind studies that provide support for Waldbott.

The profluoridationists seem to demand a high standard of proof before they will accept claims about the effects of fluoridated water on individuals. Even if particular individuals react adversely to small administered dosages of fluoride, this does not show that fluoride in water at 1.0 ppm causes the same effect. They note that fluoride is widespread in the environment — for example, it is contained in many foods — and therefore tracing adverse reactions to the fluoride in water supplies is difficult. The profluoridationists seem to require a set of definitive experiments, but few of them make clear what these definitive experiments would be.

The antifluoridationists see the studies by Waldbott and others as showing that fluoridation cannot be judged safe. They put the burden of proof on the other side. They say that profluoridationists have not conducted careful double-blind trials in an attempt to determine whether water fluoridation is causing intolerance or other adverse reactions.

The relevance of double-blind trials depends on what assumption is made about the onus of proof. The profluoridationists argue that such trials are necessary to avoid bias by those who may have falsely accused fluoridation of causing problems. The antifluoridationists argue that documented cases of allergy, intolerance reactions, or hypersensitivity are strong evidence against fluoridation until it can be proved that fluoridation is not responsible. Remember that Sutton, in criticizing the classic fluoridation trials, pointed to the lack of blind examinations of children’s teeth; in the case of intolerance reactions, it is the proponents who complain about the lack of definitive double-blind trials.

Within the medical research community, clinical randomized double-blind trials are commonly considered to be the ultimate scientific arbiter of the objective effects of a substance on humans. But such trials are not the end of the matter. Any given trial and result can be criticized and dismissed in various ways, such as by alleging shortcomings in methods used, by suggesting that the
researchers are biased, by reinterpreting the findings, or by rejecting the results as incompatible with standard findings or theories. Clinical double-blind trials certainly have not been treated as definitive in establishing allergic, intolerance, or hypersensitivity reactions to fluoride at the level involved in water fluoridation.

Another area of contention is mutations and cancer, which can be called genetic effects. There have been several claims, all rejected by supporters of fluoridation, that fluoride is responsible for genetic effects.

In the 1950s, Alfred Taylor at the University of Texas reported that cancer-prone mice drinking fluoridated water developed tumors at an earlier age than mice drinking distilled water. Ionel F. Rapaport at the University of Wisconsin in the 1950s concluded that fluoride was associated with the birth defect called mongolism, or Down’s Syndrome. Ever since the 1970s, Dean Burk and John Yiamouyiannis have claimed that fluoridation is linked to increased cancer death rates in U.S. cities. The response to the claims by Burk and Yiamouyiannis illustrates the way the issue of genetic effects has been dealt with.

Burk and Yiamouyiannis collected figures on cancer death rates in a series of large U.S. cities, both fluoridated and unfluoridated. They claimed that the cancer death rates averaged over the group of cities were the same before fluoridation but diverged afterwards, with the fluoridated group showing a 20-percent greater cancer death rate. According to Burk and Yiamouyiannis, fluoridation appears to be responsible for many thousands of extra deaths in the United States.

Unlike the issue of allergic and intolerance reactions in which individual patients can be tested, the controversy over cancer and fluoride is concerned mainly with statistics. Critics of Burk and Yiamouyiannis have said that they did not make corrections for the distribution of the population by age and sex. Alternative analyses of the cancer death rate statistics were carried out, showing no correlation with fluoridation.

Burk and Yiamouyiannis countered by saying that, contrary to their critics, they had corrected for age and sex. They criticized a contrary study by saying that it had omitted 90 percent of the data. The proponents argued, in turn, that Burk and Yiamouyiannis had not corrected their data sufficiently. As in every other area of the dispute, entirely different interpretations of evidence have been made, with no concessions to the other side.

The argument about genetic effects also takes place at the level of mechanisms. The antifluoridationists cite laboratory studies showing that fluoride can cause mutations in tissue cultures of human cells at low concentrations. Mutagens are often carcinogens or co-carcinogens. In other words, these studies suggest that a plausible mechanism exists by which water fluoridation could be associated with cancer and genetic defects. The pro-fluoridationists counter by criticizing the relevance of the laboratory studies of mutagenic effects. They say that the concentrations of fluoride in the experiments are too high, or that they do not replicate the effect of fluoride in water supplies.

There is a curious inversion of stances in the way the debate on benefits and the debate on genetic effects has proceeded. In the case of the benefits, the proponents bring forward statistical evidence of declines in tooth decay backed by experimental work showing the microscopic processes by which fluoride can inhibit decay. The opponents have challenged this position by criticizing the statistical studies on methodological grounds, while setting the experimental work aside as irrelevant unless effects can conclusively be shown for populations.

Quite the opposite set of stances is taken on genetic effects (although often by different figures in the debate). The opponents Burk and Yiamouyiannis bring forward statistical evidence of increases in cancer death rates backed by experimental work showing the microscopic processes by which fluoride can induce mutations. The proponents have challenged this position by criticizing the validity of the statistical studies, while setting the experimental work aside as irrelevant.
unless effects can conclusively be shown for populations.42

The critics of the benefits, such as Sutton and Diesendorf, believe that the evidence of risks is sufficiently strong to warrant questioning about fluoridation. Therefore, unless fluoridation can be conclusively proven to be as effective as claimed, it cannot be justified. Their implicit conclusions about risks provide a basis for their assumption about the burden of proof on the benefits.

The proponents adopt an opposite perspective. So far as they are concerned, the existence of risks has not been demonstrated. Therefore criticisms of the benefits must be conclusively proved before fluoridation can be rejected. Also, they believe that the effectiveness of fluoridation has been proved beyond any doubt, in which case a high standard of proof about hazards is required before rejecting fluoridation and its benefits.

INDIVIDUAL RIGHTS

Along with arguments about risks of fluoridation, the other staple argument in the antifluoridation case concerns individual rights. Once fluoride is introduced into the public water supply, it is very difficult to avoid ingesting it. Filters are available, but they are not cheap and, if not replaced regularly, can lead to sudden big doses of fluoride. In effect, most people are forced to have fluoride whether they need it or want it. Those who are toothless or who work in fluoride-contaminated occupations (such as aluminum smelting) drink the fluoridated water just the same as the children whose teeth are to be protected.

The individual-rights argument has been a vital one, especially in the United States where the ideology of individualism is powerful. It is an ethical and political objection, but it cannot be separated easily from what are called scientific issues.

A number of public health measures are compulsory, such as certain vaccinations and isolation of individuals with highly contagious diseases. Opponents argue that these instances do not provide a precedent for fluoridation because tooth decay is not life-threatening. Proponents then refer to laws requiring the use of seat belts in cars. Sometimes, seat belts can cause death, as in the case of fire or a car falling into water. But, so the argument goes, seat belts save many more lives than they put at risk. Hence, legislation requiring people to wear them is legitimate.

Associated with the individual-rights argument is the argument that fluoridation is unethical because the dosage to individuals is not controlled. It depends on how much fluoridated water an individual drinks. To force people to ingest an uncontrolled dosage of a substance to reduce the incidence of a nonlethal disease is seen as unacceptable by opponents.

The individual rights argument is powerful because it appeals to the concept of purity — that is, the purity of water.53 Water is seen by many people as something that should be pure and unadulterated especially, perhaps, in an age when colorings, flavorings, preservatives, and the like are added to so many foods and drinks.

The obvious and frequent response to this is that public water supplies are not pure but are chemically treated in a number of ways. Chlorination — the process by which chlorine gas is bubbled through water in order to kill bacteria — is the most well-known method of treatment. (Perhaps because the words are similar, chlorination and fluoridation are often confused.)

Opponents respond by saying that chlorination is designed to treat the water, whereas fluoridation is designed to treat the person drinking it. These opponents draw analogies with putting contraceptives or sedatives into the water supply — ideas generally considered to be ethically unacceptable — to illustrate the social danger of allowing water supplies to be used for dosing the population.

The individual-rights argument also draws strength from the existence of many alternative methods of dispensing fluoride, most of which are voluntary (see table 2.1). For example, adding fluorides to salt or sugar allows the marketing of both fluoridated and unfluori-
dated varieties, and, unlike water fluoridation, offers consumers a choice.

Table 2.1 Compulsion and Control over Dosage Associated with Several Ways of Getting Fluoride to People’s Teeth

<table>
<thead>
<tr>
<th>Fluoride vehicle (a)</th>
<th>Dosage</th>
<th>Compulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public water supplies</td>
<td>Uncontrolled</td>
<td>Compulsory</td>
</tr>
<tr>
<td>School water supplies</td>
<td>Uncontrolled</td>
<td>Compulsory for school children</td>
</tr>
<tr>
<td>Table salt (b)</td>
<td>Uncontrolled</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Sugar (c)</td>
<td>Uncontrolled</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Milk</td>
<td>Uncontrolled</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Topical application by dentist</td>
<td>Not ingested*</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Toothpaste</td>
<td>Not ingested*</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Mouthwash</td>
<td>Not ingested*</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Bottled water</td>
<td>Controlled if desired</td>
<td>Voluntary **</td>
</tr>
<tr>
<td>Tablets</td>
<td>Controlled</td>
<td>Voluntary **</td>
</tr>
</tbody>
</table>

* Except inadvertently, which does occur.
** When parents choose any method to get fluoride to the teeth of their young children, the child is seldom in a position to provide informed consent.


The individual-rights argument is a powerful one because many people are mobilized by it. In terms of logic alone, it is not automatically a weapon for the antifluoridationists. There are various ways for proponents to reply.

One response to the individual-rights argument is to say that water fluoridation is not really compulsory because people can choose to drink unfluoridated bottled water. Fluoridation, in this view, does not force people to drink fluoridated water, but imposes upon them inconvenience and financial costs if they wish to avoid it. An analogy to the financial penalty on those who choose to pay for unfluoridated bottled water is the taxation of childless people to support public schools.44

Another response is to accept the premise that there is some violation of individual rights, but that this must be weighed against the benefits from fluoride. Various analogies are used in this contention. People in a modern society must accede to some constraints on their freedoms in order to serve the general good. People accept that, in driving a car, they must stay on the correct side of the road and stop at stoplights. This may be a violation of “individual rights” to drive where and how one likes, but people accept that such “violations” are necessary for the common good.

Proponents are critical of fluoride tablets, table salt, and topical treatments for various reasons, but one important reason is that these methods of dispensing fluoride do not provide benefits to the whole community. An individual’s right not to ingest fluoride may be protected, but it is at the cost of the social rights of people in general to enjoy the benefits of fluoride. Thus, the rights argument is reversed: people should have the right to good teeth through fluoridation, and other approaches besides water fluoridation do not provide this right or benefit to everyone in the population.

The conception of “rights” has been the subject of struggle in the fluoridation debate. Although the antifluoridationists have used the rights argument much more than have the proponents, this is not necessarily because the argument over rights by logic alone supports the opponents. It may be because the propo-
ponents have kept mainly to the scientific arguments about benefit and risk, an area in which they have a near monopoly on authoritative support. The issue of individual rights and social welfare is more obviously an ethical and political issue, one the opponents can use even if they have relatively few scientists supporting them on the issues of risks and benefits.

Another means by which proponents have responded to the individual-rights argument is to say, contrary to the opponents, that fluoridation is replication of a natural process. Instead of seeing fluoridation as “artificial,” water supplies without fluoride are described as depleted. Fluoridation is simply the process of “topping up” water supplies that are “deficient” in fluoride. Large-scale water supplies for urban areas are seen by some profluoridationists as what is artificial, not the presence of fluoride. They portray water with fluoride — whether it is added or not — as healthy and natural. (While superficially plausible, I know of no actual studies of the impact of urbanization on fluoride levels to back up this argument.)

For their part, antifluoridationists consider water with added fluoride to be unnatural. They also point out that mother’s milk is normally very low in fluoride, even when the mother drinks fluoridated water. Therefore, they say, if nature knows best, fluoride for infants is inappropriate.

Thus, each side in the debate has attempted to define the concept of “natural.” This is because the wider community looks favorably on things that are “natural” and “pure.” But whether fluoridated or unfluoridated water is “natural” cannot be determined solely by reference to “nature,” which provides no unambiguous evidence. Instead, the meaning of “natural” becomes an essential part of what the fluoridation controversy has been about.

**DECISION MAKING**

A key bone of contention in the fluoridation issue has concerned how decisions should be made about fluoridation of public water supplies. This is overtly a political issue, but the role of expert knowledge about fluoridation is crucially involved. There are, in principle, a large number of different ways in which decisions about fluoridation could be made.

- Experts make a decision based on their assessments of the benefits and risks, and they have the power to implement that decision directly.
- Experts make a recommendation to a statutory authority or semiautonomous government organization that, in turn, makes a decision and implements it.
- Elected officials make a decision based on hearing evidence and arguments on scientific, ethical, and individual-rights aspects, and implement it.
- A commission of inquiry accepts submissions from all interested parties and, on the basis of these, makes a recommendation to elected officials who, in turn, make a decision and implement it.
- Elected officials make a decision, based on results of a referendum of the affected population, and implement it.
- A binding referendum is held and the result implemented.

These are only a few of the possible decision-making models. The actual reality of fluoridation decision making is usually much messier. Typically, an elected government — whether national or local — is pressured by profluoridation or antifluoridation groups to either start or stop fluoridating. Various interest groups try to exert their powers. Experts make submissions, government bodies apply pressure, and community groups and individuals write letters to newspapers. The situation becomes further confused by visiting experts, legal challenges, bans by trade unions, advertising campaigns, public meetings, and debates. If the conflicting demands are too sensitive to confront directly, the government may diffuse the responsibility by instituting an inquiry or a referendum. But the result of any formal assessment of opinion — whether an expert’s submission, a public inquiry, or a
The method by which fluoridation decisions are made is crucial to the struggle, and, indeed, part of the struggle has been between proponents and opponents each trying to ensure that the actual decision-making procedure is one that gives them an advantage.

Because the proponents have had the support of most of the acknowledged dental experts in the field, they almost always favor a decision-making method that gives these particular experts a key role. For example, most proponents would be happy with governments making decisions based on advice from authoritative bodies of dental researchers. This means that their persuasive efforts could be directed at one specific body of experts. They oppose referendums.46

The opponents have been more successful in generating support among the general public. Therefore they tend to favor decision-making methods allowing public participation, such as referendums.

Unlike the debate over the benefits and risks of fluoridation, differences involving preferred methods of decision-making are not clearly articulated in most written material about the issue. Proponents often say or imply that fluoridation is a scientific issue — in other words, the decision should be made on scientific grounds alone — but they also realize that they must, nevertheless, wage a political struggle and win the support of the general public as well as politicians. Opponents are suspicious of giving experts too much power, but they are quite willing to call upon their own experts — such as Waldbott or Yiamouyiannis.

CONCLUSION

The benefits of fluoridation, the risks of fluoridation, individual rights, and decision making: these have been the key areas of the debate. In this chapter, I have presented the arguments as if they are issues of science, logic, and assessment of human welfare by rational means. This is a narrow and inadequate framework from which to analyze the issue, as later chapters will show. But, even within this framework, it is possible to see that “arguments” do not stand outside society. They rely on a variety of rhetorical devices,47 and are embedded in systems of belief and everyday practices.

It is convenient to conceptualize arguments about benefits and risks as “tools” or “resources” that partisans can use to support their cases. For example, the reported results of the classical fluoridation trials have been a powerful resource used by the proponents. The opponents have tried to counter this with methodological criticisms. The opponents have used claims about individual rights as a tool to oppose fluoridation of community water supplies. Proponents have responded with arguments about community welfare and lack of any dangers.

Arguably, the prominence of particular lines of argument in the debate has depended on their usefulness in winning over relevant individuals — including dentists, politicians, and members of the public. Scientific details about the benefits of fluoridation have not, in the past, played a major role in the public debate, probably because the technical nature of epidemiological studies is not suited for communication to nonscientists. Issues of individual rights and community welfare are easily comprehended by nonspecialists, and so these have played a prominent role in the debate.

In each case, the arguments have been tied to wider constellations of ideas. Individual rights connotes a link to freedom of speech and religion. Community welfare may suggest a link to widely supported amenities such as clean air and national parks.

What makes a good argument is not logical coherence or social importance in some abstract sense, but logic and socially relevant realities tied to deeply felt problems and beliefs.

It is important to note that an analysis of the arguments about fluoridation, as presented in this chapter, is insufficient to promote understanding of much of the dynamics of the fluoridation controversy. Many questions remain unanswered.
How are different arguments used in relation to each other? What further resources have been used in the struggle over fluoridation? Why have most dental authorities supported fluoridation? Why has the debate been about fluoridation rather than some other facet of dental health? The following chapters will address these questions.

NOTES


2. Ibid., 67.


8. Sutton, op. cit. (note 6), 45.

9. Ibid., 97.

10. Ibid., 106.

11. Ibid., 75 (emphasis in the original).

12. Ibid., 1.

13. Ibid., 77-78.


James Morse Dunning, Principles of Dental Public Health, Cambridge, Mass.: Harvard University Press (1962), appears not to give any reference to Sutton although he had reviewed Sutton’s book not long before (Dunning, 1960, op. cit. (note 7)).


20. I thank Mark Diesendorf for this point.


22. A less colloquial phrasing is the following from J. J. Murray (ed.) Appropriate Use of Fluorides for Human Health, Geneva: World Health Organization (1986): 116. “The two other principal means of preventing dental caries [besides fluoride] are dietary control and oral hygiene. However, the role and applicability of these two measures in public health are connected with complex behavioural and cultural problems. For this reason, they are not conducive to a rapid improvement in dental health.”

23. Exner and Waldbott, op. cit.


27. Waldbott et al., chapter 8.

28. Newbrun, op. cit., 15. As noted by some critics, there were significant differences between the Newburgh and Kingston children on some tests; these have been ignored by proponents such as Newbrun.


30. Waldbott et al., op. cit., and many references therein, dating from the 1950s.


with reference to the same American Academy of Allergy statement.

33. Murray and Rugg-Gunn, op. cit.


35. For example, Royal College of Physicians of London, op. cit. Hodge, op. cit., 239, by contrast, says “Such anecdotal reports by others have also been presented.”

36. Walbott’s reluctance here may have been due to his bad experience with Hornung, described in chapter 4.


38. One exception is Taves, op. cit.


43. “Water throughout history has been perceived as the stuff which radiates purity.” Ivan Illich, H2O and the Waters of Forgetfulness, London: Marion Boyars (1986): 75-76. Illich deals with the complex cultural role of water.

44. Dunning (1962) op. cit., 372.

45. A concise exposition of this view is given by Lee A. Krimmer in a letter, Journal of the American Dental Association, vol. 88, no. 6 (June 1974): 1241-1242. “For millions of years, man’s water supply was that of running streams, lakes, rivers, wells, and cisterns. All of these forms were soil leaching, enriched with the minerals from the soil they contacted. As cities grew, man established the reservoir water supply. Reservoirs are essentially rain
water collected from short runoffs and devoid of minerals. ... God put fluoride into the water and man inadvertently took it out.”


Coherent viewpoints

The benefits of fluoridation, the risks of fluoridation, individual rights versus community welfare, decision making about fluoridation — these are four key areas involved in the fluoridation issue.

Considering these areas separately, it might seem that there is no necessary connection between conclusions reached on each one. But, when one looks at leading proponents and opponents of fluoridation, they turn out to have remarkably coherent views. That is, they either take positions supporting fluoridation in relation to benefits, risks, individual rights, and decision making, or they take positions opposing fluoridation in all these areas. If these partisans support or oppose fluoridation, they do so on all possible grounds rather than as a balance of advantages and disadvantages.

To understand the fluoridation controversy, it is necessary to go beyond an examination of the arguments, such as presented in the previous chapter, which implicitly assumes that evaluations are based solely on scientific evidence, logic, and human welfare. The coherency of viewpoints is an indication of the passionate commitments commonly found on this issue. These commitments, either for or against fluoridation, help explain the nature and style of argumentation on the issue, as well as the behaviors described in following chapters.

Coherency of viewpoints is apparent in most of the writings on fluoridation, which are easy to divide into “pro” and “anti” camps. But rather than present a detailed exegesis of written views, I will describe in this chapter my interviews in Australia with leading scientist proponents and opponents of fluoridation.

In Australia, as in other English-speaking countries, the fluoridation issue has been a major public controversy for several decades. The National Health and Medical Research Council, an advisory body made up of ad hoc expert committees, has made recommendations in favor of fluoridation since 1952. Following the early recommendations, the idea was studied by dental and health bodies in different parts of the country. Because of Australia’s federal structure, there has never been an attempt to introduce fluoridation nationally. Decisions have been made at the state level and, more frequently, at the level of individual cities and towns.

Mainly due to the initiative of individuals, a few Australian towns were fluoridated in the 1950s. Most capital cities have also fluoridated their water supplies, including Canberra (1964), Hobart (1964), Sydney (1968), Perth (1968), Adelaide (1971), Darwin (1972), and Melbourne (1977). The only capital city remaining unfluoridated is Brisbane. Thus, about two-thirds of Australians drink water with added fluoride.

The decision-making process involved varied considerably, ranging from administrative decision to extensive political maneuvering and public debate. In most cases, public debate about fluoridation was minimal in any given area in the years after a decision, whether it was pro or con. But the issue is kept on the boil by new proposals to fluoridate various towns, such as Geelong in Victoria in the mid 1980s. Similarly, decisions by the newly established self-government in Canberra in 1989 to stop and then restart fluoridation triggered an enormous public debate.

There have been many people involved in the fluoridation issue in Australia, including dentists, politicians, government bureaucrats, and “members of the public.” I set out to examine the views of knowledgeable professionals who have played an important role in the debate, with “professionals” referring mainly to scientists, dentists, and doctors. The number of such individuals who have played an important promotional or oppositional role is quite small, and has been depleted by
deaths. Those interviewed are listed in Table 3.1.

Table 3.1 Fluoridation Partisans Interviewed, Plus Their Positions at the Time of Interview

**Proponents**

**Lloyd Carr,** special advisor (Dental), Commonwealth Department of Health, Canberra; and chairman, National Health and Medical Research Council (NHMRC) Working Party on Fluorides in the Control of Dental Caries.

**Graham Craig,** associate professor, Department of Preventive Dentistry, University of Sydney; and member, NHMRC Working Party on Fluorides in the Control of Dental Caries.

**Jean Currie,** School Dental Section, Australian Capital Territory Health Authority, Canberra.

**Gerald Dickinson,** orthodontist, Melbourne; and former chairman, Australian Dental Association (Victorian Branch) Fluoridation Committee.

**Bruce Levant,** dentist, Melbourne; and former chairman, Australian Dental Association (Victorian Branch) Fluoridation Committee.

**Jack Martin,** Professor of Medicine, University of Melbourne; and NHMRC Working Party on Fluorides in the Control of Dental Caries.

**Noel Martin,** professor, Department of Preventive Dentistry; and Dean, Faculty of Dentistry, University of Sydney.

**Gavan Oakley,** dentist, Melbourne; and former chairman, Australian Dental Association (Victorian Branch) Fluoridation Committee.

**Elsdon Storey,** Professor of Child Dental Health, Department of Preventive and Community Dentistry, University of Melbourne.

**David Thornton Taylor,** orthodontist, Canberra; and former chairman, Australian Dental Association (ACT Branch).

**Keith Trayanor,** dentist, Canberra.

**Opponents**

**Mark Diesendorf,** Visiting Fellow, Human Sciences Program, Australian National University; and former principal research scientist, Division of Mathematics and Statistics, Commonwealth Scientific and Industrial Research Organization, Canberra.

**Leslie Kaufman,** retired pharmaceutical chemist, Melbourne; and former secretary, Antifluoridation Association of Victoria.

**John Polya,** retired associate professor, Department of Chemistry, University of Tasmania.

**Geoffrey Smith,** dental researcher and consultant with experience in general practice, Melbourne.


**Glen Walker,** chairman, Antifluoridation Association of Victoria; chairman, Freedom from Fluoridation Federation of Australia; former owner and then chairman of directors of a metal finishing supply company; and author of *Fluoridation: Poison on Tap,* Melbourne: Glen Walker (1982).

(Note that Jack Martin and Noel Martin are not related to the author of this book.)

I planned to interview the most important figures in the fluoridation debate in the cities of Canberra and Melbourne, plus those from other localities if convenient. Fluoridation was introduced in Canberra (Australian Capital Territory) in 1964 by administrative decision with little public debate, whereas Melbourne (Victoria) was not fluoridated until 1977 after two decades of political struggle. I hoped to uncover any divergence of opinion due to the divergent political contexts of the introduction of fluoridation in these two cities.²

To select potential interviewees, I initially contacted some well-known figures in the debates as well as state health departments and branches of the Australian Dental Association. At the end of each interview, I asked the
interviewee to name others who were prominent in the debate and who should be interviewed. It soon became apparent that I had attained almost complete coverage of the leading figures in the fluoridation controversy in Canberra and Melbourne.

Only two other individuals from these two cities are obvious candidates for the list of opponents: Arthur Amies, the former Dean of the Melbourne University Dental School, now deceased; and Edward Dunlop, a surgeon in Melbourne who declined to be interviewed. Indeed, the short list of opponents whom I interviewed constitutes an almost complete coverage of scientists, dentists, doctors, and other technical workers who have been prominent in the debate in major cities throughout Australia.

A similar near-complete coverage of leading proponents in Canberra and Melbourne was obtained. There are no widely recognized leading figures in these cities whom I did not interview; on the other hand, there was a greater number of people recommended to me for interview on the opponent side, but I did not contact every one of them. Because of the long and active struggle over fluoridation in Melbourne, there seems to be a high density of partisans there. Those knowledgeable about campaigns in other states informed me that there were relatively few to contact in Perth, Adelaide, or Brisbane.

Of the individuals listed in Table 3.1, only one — David Thornton Taylor — said he did not play an important role in the decision making or debate on fluoridation. Several — most notably Gavan Oakley and Glen Walker — are inveterate campaigners.

The interviews were carried out between September 1986 and February 1987. Bruce Levant, Leslie Kausman, and Geoffrey Smith were interviewed by telephone. The others were contacted face-to-face. The interviews lasted for 30 minutes to three hours, with the median length being one hour.

Using an interview schedule, I asked questions about the introduction of fluoridation in the relevant state, reasons for fluoridation, assessment of alternatives to water fluoridation, reasons for opposition to fluoridation, why there is little fluoridation in Europe, and appropriate decision-making procedures concerning fluoridation.

**COHERENT VIEWPOINTS**

The viewpoints of every person interviewed were highly coherent, and indeed mobilized, either in total support or total opposition to fluoridation. This included both technical issues (concerning the benefits and risks of fluoridation), as well as ethical and political issues.

The proponents were unanimous in crediting fluoridation with massive reductions in tooth decay. While figures on the order of 50 percent reduction are standard in the technical literature, two dental practitioners volunteered that the reduction in decay they had personally observed in children’s teeth would be on the order of 90 percent, if both the number and seriousness of cavities were taken into account. By contrast, only one of the opponents accepted that any reductions had been conclusively shown to be due to water fluoridation. (None ruled out that water fluoridation may have resulted in reductions in tooth decay.) They pointed to flaws in the experimental trials, and also pointed to the decline in tooth decay in unfluoridated cities, such as Brisbane.

The opponents argued that there are health hazards from fluoridation, such as intolerance reactions, for at least a small fraction of the population. They said that the possibility that fluoridation increased the cancer death rate could not be ruled out, although, as yet, the evidence was not fully conclusive. In complete contrast, the proponents denied that there was adequate evidence to demonstrate a hazard to a single individual from fluoridation. The studies purporting to show such hazards were dismissed as unsubstantiated, poorly done, or biased.

Concessions from these monolithic perspectives were so infrequent that they are worth itemizing. Smith, an opponent, said that an optimal intake of fluoride as a decay preventive has been well established. John Polya, another opponent, said that fluoride
may play some useful role in preventing decay, via individual doses for those who are not sensitive. Taylor, a supporter though not a leading proponent, noted that there is only a factor of three between 1 part per million (ppm) of fluoride in water which is optimal and 3 ppm which he said can cause unacceptable mottling of teeth, and that this factor of three is small compared to the usual factor of 100 between recommended use and harmful effects. These were the only conspicuous concessions toward the opposition’s views on benefits and risks raised in all the interviews.

One feature of the coherency of the viewpoints of proponents was a total dismissal of alternatives to the policy endorsed. One of my questions was “To what degree and why was water fluoridation promoted in preference to major campaigns for widespread use of fluoride tablets; fluoride in school water supplies; fluoride in table salt; topical applications of fluoride; improved oral hygiene; and better diet?”

Almost without exception the proponents dismissed each of these alternatives as impractical, ineffective, or even undesirable. It was said, typically, that fluoride tablets work but few people persist in giving them to their children; that school water supplies do not provide a full coverage and miss preschool children in particular; that excessive intake of salt is undesirable for health reasons; that topical applications are too expensive and do not reach the entire community; that improved oral hygiene is of limited importance for tooth decay although it benefits gums; and that achieving better diet, while desirable, is very unlikely to occur.

The reasons stated against these alternatives were not surprising, since objections have been raised to each of them in the literature. What was striking was the total rejection of all alternatives coupled with the total endorsement of water fluoridation.

For example, fluoride tablets were rejected as not providing the coverage of the community that water fluoridation offers. But, since some communities reject water fluoridation, it might be thought that tablets would be appropriate in these places, since they avoid the objection of compulsion. Again, fluoride in table salt avoids compulsion, and has been effectively implemented in Switzerland. Yet, the advantages of the alternatives in overcoming some of the primary objections to fluoridation were never mentioned by proponents.

The proponents agreed that strong efforts had been made to improve oral hygiene and diet. There were divergent opinions about whether diet had actually improved, but agreement that little could be done to dramatically alter the decay-producing aspects of Western diets and agreement that fluoridation was still necessary.

The actual words used by proponents and opponents to describe their positions are revealing. Studies have shown that scientists typically express different evaluations of evidence and knowledge through the use of different types of language. When claims about knowledge are accepted, they are typically referred to as having been derived from objective examination of material reality. The language used here is called the “constitutive” or “empiricist” repertoire. An example would be, “The early studies showed that fluoride in water significantly reduces tooth decay.”

When claims about knowledge are challenged, it is common for the human aspects of the claims to be exposed. The language here is called the “contingent” repertoire. For example, “The early investigators selected their figures in a way that favored fluoridation, while, actually, some towns with high fluoride levels had higher decay.”

I expected that advocates on each side would use the constitutive repertoire when describing their own positions and the contingent repertoire when describing the other side. As shown in the following paragraphs, this did occur regularly; but, in addition, the contingent repertoire was often used by proponents and opponents in describing views and behavior on both sides. This seems to be a product of the intensely political nature of the debate, which means that the operation of “political” factors is more overt and recognized on both sides.
Most interviewees claimed their stand was based on the scientific evidence, while denying that there was any rational basis for a contrary view. The proponents regularly described the opponents as a fringe minority. Lloyd Carr said that opponents, such as Amies and Sutton, were in the corner of a field, and that credence should be given to those in the center, including the World Health Organization, health authorities, and parliaments. When asked to account for the opposition of particular prominent figures — I specifically mentioned Amies and Dunlop — several proponents simply said they couldn’t understand it and that they never had understood what motivated antifluoridationists.

Arthur Amies was the most prominent opponent of fluoridation in Victoria for many years before his death. In view of his position as Dean of the Dental School at the University of Melbourne, both proponents and opponents said that Amies was responsible for greatly delaying the introduction of fluoridation in Melbourne where nearly one-fifth of all Australians live. The frequency and variety of contingent explanations for Amies’ stand were fascinating. It was explained to me by different proponents that Amies’ views were colored by his wife’s diabetes; that he was strongly opposed to dentistry in the United States and saw fluoridation as US in origin; and that he had a philosophical preference for treating the individual rather than using mass treatment. By contrast, Kausman and Philip R. N. Sutton, opponents who knew Amies, attributed his opposition to knowledge.

Although the participants interviewed always attributed their own stands to knowledge (the constitutive repertoire), most of them were quite open in describing why they had become involved with the topic, and, in most cases, this explanation relied on the contingent repertoire. This difference is understandable in terms of a distinction between arguments for or against fluoridation and reasons for being involved in the debate. The arguments — both for or against — were seen by most interviewees as scientific, whereas involvement in the debate was seen as political, which legitimately may be described by using the contingent repertoire.

Most proponents, without being asked, explained their own support for fluoridation and their involvement in the debate as being a result of their experience with massive decay problems, most commonly in the 1950s and as dentists or dental researchers. The dentists recounted their experiences in extracting numerous teeth — and sometimes the entire dentition — from child after child under general anesthesia, with tears from the child, the parents, and even the dentist. It was their experience of the human suffering of tooth decay that led to their support for a preventive measure.

The opponents expressed a much more varied set of motivations. Mark Diesendorf had previously been involved in campaigns on a number of environmental and health issues. Sutton said he became involved after Amies asked him to look at figures on fluoridation trials. Walker had come across fluoride in his metal finishing supply company and found it to be highly dangerous.

Contingent explanations came into their own in responses to the question “How do you account for the failure to fluoridate in some other countries, especially in Europe?” Detailed information about the reasons for lack of fluoridation in Europe is not readily available (see appendix), and so this question provided a type of Rorschach ink-blot test on which interviewees could supply speculations about the lack of fluoridation. Two respondents mentioned some sources for their information, which was mostly about Scandinavia. On the other hand, a number of respondents admitted their comments were speculative.

Explanations offered by proponents were uniform in insisting that health concerns were not the reason for lack of fluoridation. Political factors — specifically the organized efforts of antifluoridationists — were most commonly mentioned. For example, Carr said that countries have not avoided fluoridation on the basis of health, and therefore, by exclusion, there must be political reasons.
Other reasons suggested were legal obstacles, popular opposition to centralized measures (due to the experience of fascism); the low status of European dental professionals; the use of other methods to prevent tooth decay (such as fortnightly treatment of people showing a tendency towards decay); a lower level of decay; and higher natural levels of fluoride in the water. It was mentioned by a couple of respondents that the parliamentary vote against fluoridation in the Netherlands had immediately followed a claim on television by a US antifluoridationist that fluoride causes cancer. In this context Oakley said “It is nothing to do with science — it’s all politics.” This was a common view.

Opponents in their explanations gave much more weight to the rational consideration of evidence by European authorities. Kausman said that European countries had been guided by scientific advisors. Walker said that the failure to fluoridate in Europe was because their scientific communities were better educated, more inquiring, and objective. But most opponents put rational considerations in the context of contingent factors. Polya and Diesendorf each suggested that medical and scientific bodies in some countries may have been more cautious, especially of a US-based idea.

In describing the introduction of fluoridation in Australia, many of those interviewed had a great deal of information, and both proponents and opponents gave detailed accounts that usually included a strong component of contingent factors. In this chapter, I only give a few examples of how a “fact” raised on one side can be undercut by the other side.

Oakley mentioned that a local newspaper had published an antifluoridation article that said there had been a 63 percent increase in hospital admissions for kidney problems, which the author attributed to fluoride. Oakley was writing a response; he had checked with the hospital and found that the reason for the so-called increase was that there were more dialysis machines available.

In a letter to the Melbourne Age, Elsdon Storey criticized Sutton’s opposition to fluoridation. Storey noted that the judge in the Strathclyde (Scotland) court case on fluoridation had said that Sutton had made no criticism of the important Tiel-Culemborg (Netherlands) study. Sutton and Walker each spontaneously brought up this issue, noting that Sutton, in his testimony, had only been asked whether the Tiel-Culemborg study was an important one. He had replied “yes,” but had not been asked anything further about the study. In other words, he had not been asked whether he had any criticisms, which he did have.

To an outsider, these may seem like minor points, not really affecting the major issues at stake. But to those involved, small errors or alleged misrepresentations by the other side reflected the general inadequacy of those against whom they were debating.

While a few interviewees recollected the satisfaction of disputing a technical point raised by the other side, the more common experience was the intensely political nature of the debate. This was generally regarded as undesirable, and certainly seen as frustrating by nearly everyone concerned, since they believed that there was a “truth” favoring their position.

Gerald Dickinson said he would have respect for opponents if they raised constructive criticisms. But this was not the case, and, eventually, he dropped out of the issue because of the emotionalism involved. Polya was unique in being openly derogatory of nonscientist partisans involved on both sides. He characterized the proponents as having latched onto the idea of fluoridation and then being tied to it with religious fervor, whereas many of the opponents were Luddites, often with fundamentalist connections. Polya thought there was no real science involved in the debate since there was no peer group for scientific argument, and he believed that he had joined a political rather than a scientific debate.

It is common in controversial issues for partisans to attempt to associate their causes with favorable images. In this debate, the proponents regularly refer to “controlled fluoridation” — so called because the concent-
tration of fluoride in the water supply is controlled — while opponents refer to "artificial fluoridation," noting that the dosage of fluoride to people who drink fluoridated water is not controlled. The claim that fluoridation is artificial or unnatural is a staple of the antifluoridation repertoire.

What was striking in the interviews was the number of proponents who, without prompting, described water with added fluoride as more natural than its previous unfluoridated state. Graham Craig said that water fluoridation is chosen to mimic nature and to supplement depleted water. Jean Currie said that water reservoirs for urban areas are overpurified compared to natural water supplies, and contended that fluoridation is not really adding anything, but bringing the level up to natural levels. This seemed to be a common perception of fluoridation by proponents, and not just an argument of convenience. The disagreement about what is called "natural" shows that this concept can be challenged as well as struggled for. "Naturalness" does not spring unambiguously from "nature."

Perhaps the most dramatic evidence of the coherency of viewpoints came with views expressed about ethics. The objection to fluoridation that it is a violation of individual rights as compulsory mass medication for a nonlethal disease has been central to the opposition. It shapes the scientific claims of both sides.

Proponents regularly deny that there has been a single documented and authenticated case of damage to an individual’s health from water fluoridation. If it were acknowledged that, for example, fluoridation caused harmful effects in even just one of a million people, then this would have to be weighed against benefits in the form of reduced tooth decay. The argument would then become one of health costs versus health benefits.

But if there are no health costs, the argument is shifted to a different ground. There is then no apparent reason to object, and opposition seems irrational. Craig, for example, admitted that some value judgments — which he left unspecified — are involved in the fluoridation issue, but said, concerning the issue of relative risks, that there are no demonstrated risks.

Some opponents think the individual-rights argument is so important that they would oppose fluoridation even if there were no health risks. The attitude of proponents to the individual-rights argument is vastly different.

Keith Traynor said that fluoridation, like chlorination, is a health measure beneficial to the community, and individuals cannot do anything about it. Oakley took the measured view that liberties are not absolute, and that people should submit to reasonable laws for overall benefit, provided that safety is assured. Dickinson said it is ethical to have fluoridation, noting that when there is widespread disease causing pain and cost, there is a need for community health measures; an appropriate analogy is seat-belt legislation. Thus the rights issue, a key one to most opponents, carried little weight with proponents or was actually turned to their advantage.

A key question in the interviews was “What do you think is an appropriate decision-making procedure on fluoridation?” Here the views of proponents and opponents diverged again, along lines congruent with their stance on fluoridation. In Australia, the 1968 Tasmanian Royal Commission and the 1980 Victorian Committee of Inquiry have been the two most important public inquiries into the issue. Both strongly endorsed fluoridation.

With some notable exceptions, most overseas commissions and inquiries have also supported fluoridation. Opposition to fluoridation — in the United States, at least — has been more effectively expressed in referendums. When the public has been given an opportunity to express opinions on fluoridation — for example, in public debates involving meetings, petitions, and letters to newspapers — opponents are frequently much more successful than they are in formal inquiries.

Without exception, proponents favored paths in which expert bodies played a major role, advising a government that then took action and implemented the specialists’ and experts’ advice. They opposed referendums and were uniformly reluctant to support any
direct public involvement in decision making, except the involvement implicit in the election of representative government.

For example, Carr said that government — which is the voice of the people — should decide, and that the government should not make a decision without consulting the experts, such as health authorities, the National Health and Medical Research Council, and university professors. Traynor said there should never be a referendum on a public health issue because the public is not qualified to offer an opinion. Levant opposed referendums but favored a public education campaign before or after the decision to tell the public what had been done and why.

The views of proponents on decision making about fluoridation are compatible with their own situations and conclusions. Most expert bodies have favored fluoridation. They (the proponents) favor it, and many of them are the very experts whom they consider should be relied upon to play a major role.

The opponents supported community participation, usually by referendum, in decision making on fluoridation. Walker said that experts can put their cases to the people before the vote. Polya said that people should be free to choose their own medicine and health, provided that the choice does not disadvantage others. He suggested that, even with support in a referendum, fluoridation should not proceed, drawing the analogy that there should not be a referendum on religion, even though one religion may be best for the community.

The opponents still left an important role for science and expert opinion. But, contrary to the proponents, they thought that a full range of experts would not necessarily support fluoridation.

For example, Diesendorf saw value in specialists’ knowledge, but opposed a technocratic elite making decisions for the public. He contended that community decision making was necessary since political and ethical issues were involved. Sutton favored referendums in practice, but thought that, in an ideal world, fluoridation would be a scientific issue decided by appropriate scientists, including statisticians. Smith did not mention referendums, but commented that it is dangerous to legislate to enforce something that is supposed to be a scientific issue. He added that politicians should understand that no scientist has the ultimate truth.

The more diverse range of views of the opponents concerning decision making can be interpreted as reflecting two conflicting tendencies. On the one hand, they are likely to favor referendums because this has been an effective way by which fluoridation has been stopped. On the other hand, most of them hesitate to rule out the role of experts, since that is where their own role in the issue lies.

Rounding out the picture was the regularity with which both proponents and opponents criticized the decision-making approach favored by the other side. Proponents dismissed referendums, claiming that antifluoridationists would win because it is easy to scare people with allegations about poison and cancer and, anyway, people usually vote “no” in any referendum.

Two of the opponents denigrated formal inquiries. Sutton commented that judges are predisposed for judging the law and are not equipped for judging science. He also contended that they rely on the opinions of advisors and witnesses whose credibility depends partly on reputation. Polya said simply that inquiries are set up not for science but to keep people quiet. In each case, the decision-making procedure favored by the other side was undermined by using the contingent repertoire.

**Sources of Coherency**

The views of partisans who are knowledgeable about the technical issues involved in the fluoridation debate show a remarkable coherency that cuts across the common division between scientific and nonscientific issues. The topic may be the benefits of fluoride, the hazards of fluoride, alternatives to water fluoridation, reasons for the lack of fluoridation in Europe, the naturalness of fluoride in water, the ethics of fluoridation, or the most desirable methods of decision making
Coherent viewpoints on technical issues. Regardless, the partisans line up on opposite sides of the fence in a completely predictable fashion.

One possible explanation for this coherency of viewpoints is that the partisans held, prior to encountering the fluoridation issue, a set of attitudes about health risks and benefits, ethics, and decision making that they have applied to the fluoridation issue and expressed in the course of the debate. This explanation is both implausible and virtually untestable.

Probing this explanation, it may be asked: Why are there no individuals prominent in the debate who have studied the issue carefully and decided that the benefits of fluoridation are large and the hazards are negligible, but have, nevertheless, concluded that, on ethical grounds, the measure should be opposed? Why have no prominent fluoridation partisans found that the benefits are overestimated and the hazards are of concern but, nevertheless, concluded that the benefits outweigh the costs and that the decision should be made via expert committees? If knowledgeable individuals with these or other such mixtures of views do exist, they have not become prominent in the Australian fluoridation debate.

In the current and recent social climate — and speaking very generally — concern about the hazards of trace substances is characteristic of environmentalists. Support for individual rights over collective benefits is characteristic of the political right, and support for direct citizen participation in decision making is characteristic of the libertarian left. It seems most unlikely that antifluoridation partisans would have originally come to the issue with this mixture of orientations and that profluoridation partisans would have had precisely the opposite orientations. In short, it is implausible that prior sets of attitudes explain the observed coherency of views.

It may be asked: Why not test this point by asking partisans their views on seat-belt legislation, compulsory AIDS testing, nationalized health insurance, and a variety of other issues? The trouble is that for most of the partisans, the issue of fluoridation is much more significant in their lives — in some cases it is the central social issue — than the other areas to which it might be compared. As a result, personal stands on fluoridation will tend to shape views on related issues, in order to reduce cognitive dissonance. For example, views on individual rights linked to the fluoridation issue are more likely to influence views about seat-belt legislation than the reverse process.

In order to test whether views on fluoridation reflect prior sets of attitudes, one would have had to examine attitudes on a range of issues prior to an individual’s exposure to the fluoridation debate. This implies examining virtually everyone — in some cases, before the fluoridation debate even arose, since some partisans were involved with the issue from the beginning. Thus, this explanation for coherency of viewpoints is virtually untestable — at least for the case of fluoridation.

A more plausible explanation of coherency of viewpoints is the influence of the fluoridation debate itself on the partisans. Because there has been an intense public debate on fluoridation, any person with claims to expertise who speaks publicly on the issue comes under strong pressure to support one side or the other. Because most authorities — at least in English-speaking countries — favor fluoridation, any expert who voices even moderate criticism tends to be taken up by opponents as “supporting their cause.” Anyone who conspicuously spurns partisanship is unlikely to find professional or emotional support from either side. This seems likely to create pressures to join one side or the other, or to drop out of the issue.

In the camps of both proponents and opponents, there are processes that encourage the coherency of viewpoints. In the fluoridation committees of the Australian Dental Association, the explicit and sole aim is to promote fluoridation. Those actively involved in such committees scour the literature to find relevant evidence and arguments, and, in their speaking engagements, they quickly learn the most effective responses to various questions. Anyone who has debated an issue in public knows that it is difficult to stick to only a portion of the issue, especially the technical
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part. Other issues are raised in questions and, if the cause is to be promoted, effective answers must be provided.

The intense and all-consuming nature of the campaign for many of those involved is seldom apparent to people on the outside. For activists on both sides, \(^{15}\) there are talks to be given to public meetings, community groups, and the media; enquiries from the public to be answered; letters to write to newspapers; and submissions to make to politicians.

Oakley, of the proponents, and Walker, of the opponents, seemed among the most persistent and indefatigable of partisans. Interestingly, each one expressed the view that the activists, on their side, were an embattled few, with little money and insufficient people willing to take an open stand.\(^ {16}\) It is precisely this self-image of a small group of partisans making enormous efforts in the face of perceived apathy that helps mold a coherent overall perspective. Some of the scientists involved were not so heavily involved in the day-to-day struggle. Nevertheless, their views were no less coherently organized around the issue, so far as can be seen from the limited sample.

With two exceptions, the proponents reported that they had given fluoride tablets to their children. In the exceptions, the community water was fluoridated, and they supplemented this with topical fluoride treatments. Such parental action is likely to solidify belief in the benefits of fluoridation, since it would be difficult to admit to doing the wrong thing for one’s children. By contrast, the opponents had not given fluoride tablets to their children, similarly making it more difficult to admit that they were wrong in their beliefs.

Another factor promoting uniformity of viewpoints is the reliance on material from overseas by both proponents and opponents. Certainly, endorsements by dental and medical associations from other countries are regularly cited by proponents, whereas critical work is cited by opponents. But it is not clear how much the use of this material actually influences the coherency of positions. Obviously, not all overseas material is used, and what is used must be adapted for Australian conditions and audiences.

One factor that reflects the coherency phenomenon as well as maintains it is the lack of informal personal contact between proponents and opponents. It would seem that the most regular contact between those on opposite sides occurs during hearings or debates on fluoridation — for example, before local councils. There seems to be little free discussion of the issues. Symptomatic of this is the comment by Sutton that no one in the Melbourne University School of Dentistry approached him to talk about fluoridation during his ten years there, although the school included many supporters of fluoridation, including the prominent proponent Storey.

While contact between partisans on opposite sides is uncommon, interaction between those on the same side is frequent and can be intense. Consultation can occur to check facts, prepare arguments, coordinate talks, or compose letters to newspapers and journals, and so forth. It is not surprising that interaction between sympathizers is common. Some of the opponents reported receiving considerable correspondence from around the world. Naturally, most of it is from other opponents.\(^ {17}\)

In organizing speakers for public meetings, preparing testimony for formal hearings, or arranging publicity material for the media, each side promotes those individuals who are most effective in supporting the overall case. Those with intermediate, complex, or ambivalent positions receive little encouragement to take leading roles. In Edward Groth’s words, there is a “natural selection for extremist leadership.”\(^ {18}\) Only those tough enough and committed enough to stand up to abusive attacks and to suppress self-doubts are likely to stay in the campaign.

Another factor is the lack of criticism by people on one’s own side. Pro- and antifluoridation scientists have seldom openly criticized the inaccuracies, exaggerations, and simplifications made by activists on their own sides, although they may privately deplore these shortcomings. Usually, they try to maintain scientific integrity by attacking mistakes made
by those on the other side, while presenting their own cases in as persuasive a manner as possible yet compatible with their assessments of the evidence. Peer-group pressure restrains individuals from criticizing others on the same side and thus breaking ranks since, in the context of the controversy, this would, indeed, seem to help the other side — at least in the short term.

Does it make sense to analyze separately the views of partisans on science, ethics, and politics? My conclusion, based on interviews with Australian fluoridation partisans, is that it does not. The coherency of viewpoints most plausibly derives from engagement in a public debate on an issue with both scientific and political dimensions. To resist pressures for coherency within the debate would mean not so much individual cognitive dissonance but rather social dissonance — attacks from both sides and pressures to take a stand.19 For the technically knowledgeable partisans discussed in this chapter, it makes little sense to isolate views on the benefits or hazards from opinions on individual rights, because beliefs on the whole array of issues are made coherent by the debate itself.

The partisans themselves often distinguish between science and politics, usually in a way that aids their own argument. The distinctions they make can be described as being “socially constructed.” For the purposes of social analysis of partisan viewpoints, it seems much more useful to set aside their usual distinctions between science and politics and to analyze their viewpoints on a whole range of topics. In this way there is less illusion that views are separately formed on the merits of the case, whether in science, ethics, or politics. Rather, what seems to happen is that individuals make a global judgment about fluoridation in the context of the polarized debate. Then, their stance for or against fluoridation promotes a coherency of views on the separate arguments, cutting across the distinction between scientific and nonscientific factors.

**FLUORIDATION PARADIGMS?**

The coherency of viewpoints is compatible with the idea that thought and behavior on the fluoridation issue are guided by two contrary paradigms.20 The concept of “paradigm” here is a liberal adaptation of Thomas Kuhn’s notion of paradigm as a complex of ideas and practices that guides the routine performance of scientific research within specified areas, such as the paradigm of Ptolemaic or earth-centered cosmology that was superseded by the paradigm of Copernican or sun-centered astronomy.21

To speak of two paradigms in a single area is to imply a situation of conflict or crisis. The profluoridation paradigm is basically that water fluoridation is highly beneficial and completely safe and, hence, socially desirable. The antifluoridation paradigm is essentially that fluoridation is harmful to some people, unethical, and possibly not proven to be especially beneficial and, hence, socially undesirable.

Using this picture, partisans collect and interpret evidence starting from the presuppositions of their own paradigm, and mobilize arguments to support it. Whether one calls it a paradigm, an exemplar, a world view, or a coherent position, the value of this concept is that one can predict with considerable accuracy the arguments of a partisan by knowing the answer to a single question: “Are you for or against fluoridation?”

**NOTES**

Most of the material in this chapter is adapted from Brian Martin, “Coherency of Viewpoints among Fluoridation Partisans,” *Metascience*, vol. 6, no. 1 (1988): 2-19.


2. An excellent account of the politics of fluoridation in Victoria is given by Brian W. Head in “The Fluoridation Controversy in Victoria: Public Policy and Group Politics,”
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Australian Journal of Public Administration, vol. 37, no. 3 (September 1978): 257-273. For other states, there are no equivalent accounts although Wendy Varney provides considerable documentation, especially for New South Wales, in Fluoride in Australia: A Case to Answer, Sydney: Hale and Iremonger (1986).

Carr described the introduction of fluoridation in Canberra as a process in which the four relevant Commonwealth ministers — Health, Australian Capital Territory, Works, and Attorney-General who are elected parliamentarians with briefs similar to US cabinet members — each took advice from their departments which, in turn, consulted their experts. After discussion in cabinet, the government took a decision.

Traynor described the Canberra decision in this way: Traynor was the dentist who treated Harold Holt, the federal Treasurer. The federal president of the Australian Dental Association suggested to Traynor that he raise the question of fluoridation for Canberra with Holt. Via Holt, a visit was arranged between the Minister of Health and Traynor along with Peter Lazar, director of the Dental Health Education and Research Foundation. Later, Lazar and Traynor met with Prime Minister Robert Menzies, who was favorable. (Earlier, they had approached the opposition Australian Labor Party’s spokesperson on health, who was also agreeable.) Shortly afterward, Menzies put the motion for fluoridation in parliament.


5. A proponent whom I didn’t interview told me he had heard it said that Amies was more likely to obtain ego gratification from opposing fluoridation than from scientific work, at which he was mediocre.


11. Smith, whose comments concerned the role of scientists, is a possible exception.

12. Concerning the Tasmanian and Victorian inquiries, Varney, op. cit., 23, states along this line that “Judging from the circumstances and conduct of both of these inquiries, it is doubtful that their chief purpose was to probe into, and weigh up, the conflicting evidence. Rather they were to convey an image of neutrality and open-mindedness on
the part of the respective governments and so to allay public fears by supposedly having thoroughly investigated the matter prior to government’s final decision.”


16. Varney, op. cit., points out that the proponents in Australia are backed by the dental and medical professions, the federal and most state governments, and several major industries. But, from the point of view of profluoridation partisans, this does not translate into volunteers to carry out the day-to-day legwork on the issue.

17. The argument here is compatible with standard ideas in social psychology. See, for example, George Cvetkovich, Steve R. Baumgardner, and Joseph E. Trimble, Social Psychology, New York: Holt, Rinehart and Winston (1984): 176-209; and Kenneth J. Gergen and Mary M. Gergen, Social Psychology, New York: Springer Verlag (Second edition, 1986): 158-191. Attitudes based on direct experience (such as attending meetings, speaking, or writing letters in the fluoridation debate) are more likely to be salient and central to attitude structures, and more likely to cause a reduction in dissonance with related but peripheral attitudes.


19 To my knowledge, Geoffrey Smith is the only one of those interviewed who has been criticized by both proponents and opponents.


PART I: ENDORSEMENTS AND DEBATES

Only to a limited extent has debate on fluoridation proceeded on the basis of pure discussion of claims about knowledge. Almost always salient has been who has made the claims. If a doctor or dentist makes a statement about tooth decay it is given more credence than exactly the same statement made by a layperson. If a professional body, such as the American Dental Association, makes a statement, it is given more credence than exactly the same statement made by a single dentist or even a group of dentists.

**Endorsements**

Authoritative backing has been a key to the debate on fluoridation. In the 1940s in the United States, the most influential relevant bodies — the United States Public Health Service (USPHS), the American Dental Association (ADA), and the American Medical Association (AMA) — had not endorsed fluoridation. The promoters of fluoridation devoted much of their efforts towards convincing the key people in these bodies of the value and need for early endorsement.

In the late 1940s, the USPHS adopted a policy of delay: it would not endorse fluoridation on the basis of information then available. This stand by the premier authority provided valuable support for opponents of fluoridation. The promoters of fluoridation devoted much of their efforts towards convincing the key people in these bodies of the value and need for early endorsement.

In the late 1940s, the USPHS adopted a policy of delay: it would not endorse fluoridation on the basis of information then available. This stand by the premier authority provided valuable support for opponents of fluoridation. As historian Donald McNeil said, “Recommendations for delay by the national organizations became potent weapons in the hands of local opponents of fluoridation.” The opponents could justify their stand by pointing to caution by the USPHS and the ADA. This added authority, but not extra evidence or arguments, to the opponents’ position.

John J. Frisch, Francis Bull, and other leading proponents of fluoridation kept heavy pressure on the top figures in the USPHS throughout the late 1940s. Finally the USPHS acquiesced. In May 1950, it announced its support for fluoridation. This is generally acknowledged as a turning point in the struggle. With the USPHS taking a stand, the ADA added its support. It, too, had been the subject of intense lobbying and pressure for some years.

Although the evidence about the risks and benefits of fluoridation was essentially the same before and after the endorsements by the USPHS, the ADA, and the AMA, the resources available to the proponents and opponents were vastly changed. The opponents, previously able to cite the stands of these organizations to justify their reservations, now had to confront proponents backed by their endorsements.

Prior to the endorsements, the proponents were overtly political in their approach. Frisch “was often impatient with his professional colleagues who felt the battle should be waged on a factual and dignified level.” He believed that political campaigning methods were needed on this political issue. The intense and unrelenting campaign by Frisch and his colleagues was important in obtaining the endorsements for fluoridation. But, once the endorsements were obtained, the style of the confrontation changed. Now, it was the turn of the opponents to be overtly political while the proponents portrayed themselves as strictly scientific and following the best expert advice.

Ever since 1950, the weight of authoritative backing has strongly favored fluoridation. Professional endorsements have been used repeatedly as a prime argument for fluoridation, as is apparent from perusing just about any piece of promotional literature. In this situation, it is the opponents who appear overtly political. In order to promote their case, they have to challenge the “authorities.”
Frank J. McClure’s book *Water Fluoridation: The Search and the Victory* illustrates the heavy use of endorsements. In the chapter on “Approval,” he quoted some of the early statements for fluoridation made in the 1940s. After outlining the early endorsements by professional organizations in the early 1950s, McClure stated, “Fluoridation has been given official approval by virtually all national and international health and professional organizations.” He proceeded to quote statements from ADA, AMA, the American Association for the Advancement of Science (AAAS), the American Federation of Labor and Congress of Industrial Organizations, the American Water Works Association (AWWA), and the American Institute of Nutrition (AIN). He then listed 34 American and 15 British organizations approving fluoridation. He quoted from the Canadian Dental Association (CDA), and quoted “additional statements” from eight individuals or organizations. This section of McClure’s book is testimony to the importance he placed on endorsements.

Such endorsements often are used as a general recommendation of fluoridation. They serve as shorthand. Instead of giving a detailed account of the arguments for and against the measure, the endorsements are cited as evidence of the conclusion of “those who should know.” This is a usual procedure in many areas of health and technology: professional endorsements of safety are taken to indicate that experts have investigated a product or practice and found it safe.

For the opponents of fluoridation, the extensive endorsements are a major stumbling block. There are several ways they have responded. One is to find individuals or groups who openly criticize fluoridation, or who refuse to make endorsements. The work of opponent scientists — such as George Waldbott and John Yiamouyiannis — is repeatedly cited.

Another way to criticize endorsements is to try to undermine the process of endorsement itself. One line of argument is that the numerous endorsements do not represent independent evaluations of the important issues. Bodies such as the AIN did not carry out their own research or comprehensive assessments of the research literature. Instead, most of the endorsements have been made on the basis of earlier endorsements by a few key organizations, in particular the USPHS and the ADA.

At best, endorsing bodies relied on advice from a small number of experts, almost all of whom were committed promoters of fluoridation. Furthermore, opponents alleged that key promoters applied pressure on professional societies for rapid — and hence, less carefully considered — endorsement. One such promoter was H. Trendley Dean in the case of the AAAS, of which he was a former president. The opponents saw a “bandwagon” or “snowballing” process, in which organizations concluded that, if the “real” authorities were for it, it must be all right.

Opponents also alleged that some endorsements have been “pushed through” without proper concern for due process, not to mention the arguments. Concerning the endorsement of fluoridation by the World Health Organization in 1969, Waldbott, Albert W. Burgstahler, and H. Lewis McKinney stated that “during the final hours of the session, when only 55 to 60 of the 1,000 delegates from 131 countries were still present, all bills that had not been accepted were collected into one and voted upon, including a statement on fluoridation.” (The profluoridationists could complain of a similar lack of due process in some of their defeats, such as the Swedish Parliament’s repeal of the Water Fluoridation Act in November 1971.)

There remains the further problem that the World Health Organization has re-endorsed its profluoridation stand, a fact seldom mentioned by antifluoridationists. One response would be to say that it is much easier to re-endorse a stand than to reverse it.

While the argument about “snowballing” and contrived endorsements may undercut the persuasiveness of the great number of endorsements, it does not explain away the important early endorsements. The opponents have two lines of attack here.

First, they argue that these endorsements were pushed through by a small number of
profluoridation activists, and do not represent the opinion of all the members of the organization. Second, they assert that the endorsements are not based on original research by the endorsing bodies. They are simply statements by groups claiming that the research points to a particular policy.

This second line of argument leads to the conclusion that people should be looking at the evidence rather than at endorsements, and this is precisely the approach favored by the opponents. They usually prefer to deal directly in the arguments about benefits, risks, and individual rights, whereas the proponents often refer to endorsements.

This difference does not arise because opponents, by the nature of their stand, have some special commitment to informing the public about the actual issues (although some opponents do have a commitment to this). Rather, the opponents cannot use the resource of endorsements because so few prestigious bodies oppose fluoridation. If dental associations opposed fluoridation, most opponents would use endorsements as readily as do the proponents. This is clear from the regular reference by opponents to those few professional bodies that do openly oppose fluoridation.

Widespread authoritative endorsement allows some proponents to go a step further and deny that there is any legitimate scientific debate at all. For example, Conrad A. Naleway of the ADA wrote in 1988 that “there is no scientific case to support the antifluoridation position.”¹⁹ In denying the existence of scientific debate, proponents are implicitly stating that all knowledgeable people support fluoridation and that anyone who opposes fluoridation must, therefore, be uninformed, politically motivated, or in some other way “unscientific.”

In 1978, the magazine Consumer Reports ran a two-part article attacking opponents of fluoridation. The article concluded with the statement that “The simple truth is that there’s no ‘scientific controversy’ over the safety of fluoridation. The practice is safe, economical, and beneficial. The survival of this fake controversy represents, in CU’s [Consumers Union] opinion, one of the major triumphs of quackery over science in our generation.”¹⁰

What is only implication in other statements is spelled out here: there is no scientific debate; therefore, opponents are quacks.

It is revealing that the claim that all experts support fluoridation and that there is no scientific debate became routine only after the endorsements by professional bodies in the early 1950s. These endorsements did not change the scientific evidence then available, but they did eliminate a major resource used by the opponents — namely, that authoritative bodies had not endorsed the measure.

To Debate or Not to Debate

In the struggles over fluoridation, there have been many opportunities for the issues to be debated — for example, in public meetings, in local government meetings, and before community groups. Profluoridationists often have refused to openly debate antifluoridationists in such settings when they consider that debating will hurt their campaign. The reason they give for this is that there are no valid grounds for opposing fluoridation, and, therefore, any debate can only give credibility to the opponents by acknowledging that there is something worthy of debate. Refusing to debate can be interpreted as an attempt by those with a near monopoly on credibility — in this case scientific or professional credibility — to deny any of it to the opponents.

In 1952, Charles Eliot Perkins, a biochemist and physiologist opposed to fluoridation, described how proponents refused to appear on a radio forum in Washington, D.C. shortly after the city’s water supply had been fluoridated. Perkins concluded that “The professional proponents of fluoridation, as a rule, refuse to discuss the subject in public meetings or debate fluoridation with anyone who opposes it in public forums.”¹¹ This has remained the pattern ever since.

In 1979, the Society for Social Responsibility in Science in Canberra, Australia, organized a debate on fluoridation and cancer between fluoridation supporter Roland Thorp and fluoridation opponent John Yiamouyian-
nis. Afterward, Dr. Peter Cooper, chairman of the Australian Capital Territory Cancer Society, wrote an article and letters for the *Canberra Times* denying any link between fluoridation and cancer, and calling fluoridation a “nonissue.” When challenged by Mark Diesendorf to a public scientific debate on the issue, Cooper replied that Diesendorf “doth rant and rave, and mightily stir to keep the fluoridation pot aboiling.” Then, he declined to debate.

Robert Isman, in an often-cited article, “Fluoridation: Strategies for Success,” which was published in 1981 in the *American Journal of Public Health*, commented: “Several authors have recommended that debates be avoided and I concur with this recommendation. This is little to gain and much to lose from debating an emotional issue like fluoridation. A debate simply serves to give more credibility to fluoridation opponents.” Prominent proponent Ernest Newbrun concurs. He says that he normally refuses to debate because “it is my policy not to give credibility to antifluoridationists.”

In 1985, Michael W. Easley commented similarly in an article “The New Antifluoridationists” in the *Journal of Public Health Dentistry*. He wrote, “Armed with volumes of scientific literature and lists of endorsements, eager proponents of fluoridation too often are trapped into consenting to public debates on this sociopolitical controversy. Almost nothing can be gained by debating. Regardless of which side is successful in presenting the best argument, the mere fact that the debate even took place conveys to the public that a legitimate scientific controversy exists.”

This does not mean that the proponents do not campaign at all. They conceptualize the issue as being in two parts: a scientific part and a political part. The scientific part, they believe, consists of scientific findings that contain no basis for opposing fluoridation. This is the foundation for the claim that there is no scientific debate. The political part of the issue arises from the existence of opponents who are motivated for nonscientific reasons. This political opposition must be countered, and thus many of the proponents counsel the waging of a political struggle for fluoridation.

Easley concluded, “Foremost is the need to recognize and accept the realization that fluoridation is no longer strictly a scientific or legal issue, but that it has become predominantly a political issue.” Part of the political struggle is the refusal to debate, thereby denying the opponents any credibility.

Unfortunately for the profluoridationists, refusal to debate can raise problems. Ernest Newbrun commented that “Whether or not to participate in radio or TV talk shows or debates on fluoridation poses a real dilemma for the dental researcher.” Participating in and responding to antifluoridation arguments can give them legitimacy, whereas “by refusing to appear on such programs, there is always the risk of permitting the antifluoridationists free rein.”

Another problem is that, when supporters of fluoridation refuse an open invitation to debate, this often is seen by citizens as arrogance. As analyzed by Raulet, professionals such as dentists and physicians promoting fluoridation can take either the role of experts or partisans. Many have attempted to fill both roles, and this sometimes leads to difficulties. As experts, they can act as authoritative sources of information but are open to the charge of arrogance in refusing to debate. But if they enter the debate as open promoters, the role of expert knowledge in support of fluoridation is undercut.

To be an authoritative source of information while not openly promoting fluoridation means taking a low-visibility role. The scientist who publishes technical papers in specialized journals or the dentist who answers questions from patients falls into this category. This stance draws its strength from the image of the objective and socially concerned professional who has no apparent vested interest in a particular course of action. It is precisely from not being openly partisan that the role of the objective professional draws its strength. Ideally (for those who support fluoridation), this would be all that is required to create a climate leading to the implementation of fluoridation.
While this stance is possible for some supporters of fluoridation, it has seldom been adequate to introduce and sustain the measure. The opponents of fluoridation have been open and vociferous in their campaigning. A low-key stance is not enough to counter such opponents. Consequently, some supporters of fluoridation have had to be openly political as well, and this has included many dentists, doctors, and scientists.

Partisans have been involved in lobbying fellow professionals and politicians, speaking at community groups, writing letters to newspapers and journals, writing general interest articles, speaking on radio and television, debating, fundraising, passing out leaflets, and a host of other activities. Dentists, doctors, and scientists supporting fluoridation as partisans can be effective via their activism, but, at the same time, many of them rely on their professional role to give status to their views beyond that of a lay partisan. But their activism can undercut the advantages of professional status to some extent, since many of the methods of campaigning are widely perceived to be incompatible with objectivity.

Note that the two roles of expert and partisan are only perceived to be divergent. It is quite possible for an “objective source of information” to be an effective proponent — for example, by publishing scientific papers or teaching dental students in ways which favor a particular conclusion. Likewise, it is possible for an active partisan to be extremely careful with the evidence and arguments, more so than those who are not partisans.

In each case, the role of expert and partisan is not inherent in the knowledge or social role, but depends on the interaction of behaviors and beliefs. The social construction of an expert or partisan depends to a great extent on the ways, or lack of ways, in which opponents can attack.

For example, it is very difficult for the opponents to criticize those who make contributions only in specialized scientific journals. Such criticism tends to be highly technical — as in the case of Sutton’s critique of the classic fluoridation trials — and, hence, is not very useful for public campaigning. By contrast, those who make the same points in newspapers or on radio are much more vulnerable to attack. When translated out of the technical context, the same points are subject to criticism in a way that would not be permissible in a scientific journal.

It is also important that partisans can be attacked because they are partisans. The opponents can claim, with apparent justification, that fluoridation is not just a scientific matter, but is being promoted because of various vested interests. The partisan promotion of fluoridation — made necessary by the partisan opposition — thus must be masked as much as possible. This is because the rhetoric of promotion sounds incompatible with the language of objective science, and opponents can use this ostensible incompatibility to attack the proponents.

Promoting Fluoridation

An early and revealing example of this dynamic centers around a talk given by fluoridation proponent Francis Bull in 1951, at the Fourth Annual Conference of State Dental Directors with the USPHS and the Children’s Bureau, in Washington, D.C. Remember that Bull was one of the leading figures behind the push for fluoridation in the 1940s, a push which led to the key endorsements in 1950 and 1951. In his talk titled “Promotion and Application of Water Fluoridation,” Bull was essentially telling new supporters how to sell fluoridation.

Bull was quite candid in his talk. Unknown to him, there was a stenographer present making a complete record of the proceedings. Later, antifluoridationists obtained a copy, and, ever after, they have been quoting Bull out of context in order to damn the promotion of fluoridation.

Bull spent considerable time describing how to answer objections to fluoridation. I think the first one [objection] that is brought up is: “Isn’t fluoride the thing that causes mottled enamel or fluorosis? Are you trying to sell us on the idea of putting that sort of thing in the water?” What is
your answer? You have got to have an answer, and it had better be good. You know, in all public health work it seems to be quite easy to take the negative. They have you on the defensive all the time, and you have to be ready with answers. Now, we tell them this, that at one part per million dental fluorosis brings about the most beautiful looking teeth that anyone ever had. And we show them some pictures of such teeth. We don’t try to say that there is no such thing as fluorosis, even at 1.2 parts per million, which we are recommending. But you have got to have an answer. Maybe you have a better one.23

Bull’s comments suggested to many opponents of fluoridation that the proponents were trying to hoodwink people about the problem of fluorosis by calling mottled teeth “beautiful looking teeth.”

Waldbott certainly took this view, saying “Bull instructed his colleagues to describe mottled teeth to the public and to the profession as ‘egg-shell white’ and ‘the most beautiful looking teeth that anyone ever had,’ even though these teeth are known to turn brown and brittle in later years.”24

The context of Bull’s talk was his confidence in data showing that fluoridation is highly beneficial and harmless. For Bull, fluoridation, unlike all previous public health measures, “has absolutely no bad connected with it.”25 Therefore, the issue was how to promote it. Language and images are important, and part of this is the language used to describe mottled teeth.

Bull continued by dealing with another perception of fluoridation.

And, incidentally, we never use the term “artificial fluoridation.” There is something about that term that means a phony. The public associates artificial pearls or artificial this or artificial that with things that are not real or genuine. We call it “controlled fluoridation.”26

To this day, a fairly reliable test of a person’s stance on fluoridation is whether they call it “controlled” fluoridation, as do the proponents, or “artificial” fluoridation, an expression favored by the opponents. The choice of language is a crucial part of the debate.

Bull continued:

Incidentally, we never had any “experiments” in Wisconsin. To take a city of 100,000 and say, “We are going to experiment on you, and if you survive we will learn something” — that is kind of rough treatment on the public. In Wisconsin, we set up demonstrations. They weren’t experiments.27

Bull’s advice has been taken up by proponents ever since. Sutton in his critique of the “classic trials” argued that they were experiments. Sutton’s critics argued that fluoridation had already been proved, and that the trials were demonstrations. Here is a case in which Bull’s advice on promoting fluoridation (and that of others) entered into the “scientific” area of disputes over the validity of the trials.

The next quote from Bull shows how much difference context makes.

… this toxicity question is a difficult one. I can’t give you the answer on it. After all, you know fluoridated water isn’t toxic, but when the other fellow says it is, it is difficult to answer him. I can prove to you we don’t know the answer to that one, because we had a city of 18,000 people which was fluoridating its water for six or eight months. Then a campaign was started by organized opposition on the grounds of toxicity. It ended up in a referendum and they threw out fluoridation. So I would hate to give you any advice on that deal [Laughter]. It’s tough.28

It is easy, and tempting for opponents, to take this statement out of context — especially the part about “this toxicity question is a difficult one. I can’t give you the answer on it” — and conclude that Bull was admitting that the proponents, at least in 1951, didn’t know for sure whether fluoridation might have toxic effects.
But this is not what Bull was saying. He stated, after all, that “you know fluoridated water isn’t toxic.” Bull was concerned about promoting fluoridation, and he was raising the problem that there was no good argument or turn of phrase to counter claims of toxicity. When he said “we don’t know the answer to that one,” he meant that there was no answer that was effective for public campaigning, rather than no answer at all. He was seeking an answer, such as calling mottled teeth “beautiful” or referring to controlled fluoridation.

The point is that promotion assumes — or sometimes ignores — the validity of what is to be promoted. In an honest and open talk, a promoter describes the good and bad ways of going about the promotion. But “honest and open talk” is dangerous if it gets into the wrong hands.

Bull also said, “Now, why should we do a pre-fluoridation survey? Is it to find out if fluoridation works? No. We have told the public it works, so we can’t go back on that. Then why do we want a pre-fluoridation survey?”

This quote seems to be the most damning yet. Bull appeared to be saying that the promoters cannot go back on their claims that fluoridation works. But the context gives a different story.

Bull advocates making prefluoridation surveys of tooth decay, and says that the fluoridation committee of the state dental society can assist in doing this. After the previously quoted passage, he went on to say that the point of a prefluoridation survey would be to show, later on, the effectiveness of fluoridation in preventing tooth decay as insurance against possible future campaigns to stop fluoridation.

Once again, Bull was assuming that fluoridation is a good thing, and was simply presenting his views as to how it could best be promoted. He was advocating prefluoridation surveys as insurance against subsequent attempts to stop fluoridation. In this quote, he was telling others not to fall into the trap of thinking — or saying — that a prefluoridation survey is intended to find out if fluoridation works. If anyone said that, it could be used against them by opponents.

It is clear from this example why statements about how to promote fluoridation are better left out of the public eye, just as the candid discussions of the designers of advertising copy would be damaging to the product concerned.

Bull’s talk is part of the large literature on how to promote fluoridation. Annabelle Bender Motz, in a 1971 review article published in a collection entitled *Social Sciences and Dentistry*, outlined some of the recommendations stemming from this literature. First, the community to which fluoridation is to be introduced should be studied closely, noting demographic characteristics, the political system, and so forth — all in an effort to plan an effective strategy.

Second, fluoridation should, if possible, be introduced through legislation or administrative action since popular participation, for example through a referendum, often leads to the rejection of fluoridation.

Third, if popular involvement cannot be avoided, grassroots support for fluoridation should be developed through community groups and locally influential people. This might involve Rotary clubs, mothers’ groups, health associations, trade unions, and many other organizations.

Fourth, “confrontations whether in the form of panel discussions, public debates, or referenda” should be avoided. Here, Motz referred to several social-science studies. For example, “[H.] Nathan and [S.] Scott have shown that confrontations give the anti-fluoridationists the stamp of legitimacy on a par with that of the recognized community leaders and organizations.”

Fifth and last, the role of the “health publicist” should be developed. Such people would, for example, use knowledge about a community to plan a program to introduce fluoridation or some other health measure. By being neither a scientist nor a medical practitioner, the “health publicist” may be able to avoid being typecast as an arrogant professional.
The large body of social-science research suggesting how to best promote fluoridation is based on the proponent claims that fluoridation is a scientific issue and that there is no scientifically credible opposition to it. The idea of creation of the “health publicist” assumes that the professional experts will decide what is best for the community, and then this will be “sold” to the community by using the best selling techniques that social science can provide.

From the point of view of the opponents — especially those who are scientists — the refusal to debate is a denial of all that is proper.

PART II: RESPONDING TO SCIENTIST OPPONENTS

Without endorsements by the major professional bodies, the best the opponents have been able to do is cite a few organizations that have opposed fluoridation and a number of individual professionals who are critical of fluoridation. Although the number of these individuals is very small compared to the total number of dentists and doctors formally represented by profluoridation professional bodies, their critical perspectives are vitally important because they challenge what would otherwise appear to be unanimous professional support for fluoridation.

The opposition to fluoridation has included a large number of “extremists.” In the 1950s in the United States, the John Birch Society was involved, as were some other right-wing and anticommunist groups. The opposition has also included members of some religious groups — such as Christian Scientists — as well as naturopaths, chiropractors, and others considered by the medical profession to be fringe practitioners or “quacks.” In other words, “reputable” bodies — such as the ADA — supported fluoridation, while “fringe” bodies and individuals opposed it.

This, at least, was the picture painted by the proponents. It is a picture quite favorable to the proponents, since it suggests that rational and respectable people support fluoridation, whereas opponents are found only among “fringe” groups. The rhetoric of many fluoridation opponents often helps to confirm this view. Nonscientists who are opponents frequently sound extreme — but so, also, do some of the scientists.

Charles Eliot Perkins in his 1952 booklet *The Truth About Water Fluoridation* included numerous scientific arguments, but these are interspersed with political commentary with extreme-sounding claims. Perkins concluded that “It is common knowledge that artificial water fluoridation is a technique in mass control through mass medication, which is an integral part of Communist philosophy.”

Frederick B. Exner, a medical doctor and leading opponent of fluoridation in the 1950s, wrote that, in convincing people that fluoridation is completely safe, “the primary tools have been equivocation and prevarication. Outright lies are rarely used except when so tightly cornered under cross-examination that there is no other way out.” Exner referred to the promotion of fluoridation as “an incredible story of chicanery and malfeasance.” He attributed fluoridation to a totalitarian philosophy, both in those “who sincerely believe in the *Führer* principle” and “‘do-gooders’ who promote totalitarianism through good-intentions-gone-crosswise.”

Philip E. Zanfagna, a doctor and coauthor of a book opposing fluoridation published in 1974, wrote that “While the fluoridation travesty is in progress, Americans are ingesting more poisonous fluorides (and other dangerous chemicals) with their food, water and from polluted air than any other people on earth. Related to this consumption, the national incidence of heart attacks, cancer, crippling arthritis, infant deaths, and enzyme-deficiency diseases continues to rise.”

Zanfagna’s coauthor, writer and activist Gladys Caldwell, used more colorful language, describing fluoridation as “the most disastrous and costly consumer fraud of this polluted century. Hundreds of millions of tax dollars have been spent to programme an entire generation to salivate like Pavlov’s dogs when the word fluoridation is mentioned.”

Glen Walker, a leading Australian antifluoridationist, concluded his long and
vehement book on the topic with the statement that “Yes fluoridation is a hoax!”

Robert Mick, a New Jersey dentist and researcher, and highly visible opponent, said that “Hitler was a Boy Scout compared with the United States Public Health Service … To be selected by the United States Public Health Service for an experiment is a CRIMINAL CONSPIRACY surpassing acts of those Nazis who were hung for selecting humans for experiments.”

Other statements similar to these would be easy to list. In each case, undoubtedly, those making the statements would argue that they are being perfectly accurate. But others may be repelled by the intemperate-sounding language, and be drawn to the proponents’ categorization of all opponents as “cranks.”

This picture has always been complicated by the presence of some orthodox, mild-spoken, and otherwise respectable professionals — dentists, doctors, and scientists — who are critical of fluoridation. While some of them — such as Exner and Mick — on occasion used extreme-sounding language, others, such as Albert Burgstahler and John Colquhoun, have been more restrained.

The very existence of such individuals undermines any suggestion of professional unanimity. Proponent Sheldon Rovin recognized the problem: “There are increasing numbers of ‘credentialed opponents’ lurking about in fluoridation matters. One or two dentists or physicians coupled with a few scientists who are opposed to fluoridation can stymie even the best organized and conducted fluoridation campaign.”

The promoters of fluoridation have responded to these critics in various ways. One response has been to criticize their arguments, as described in chapter 2. But a response of logical and cautious criticism is not always enough to undermine an opponent’s credibility.

Further — or different — measures have been taken in many cases. Rovin said, “Ways to neutralize these people are limited. The choices are to ignore them, assail their motivations, or drown them out by enlisting large numbers of dentists and physicians on behalf of the issue in a manner highly visible to the public. Of these, the third is obviously the best choice.”

But, quite often, methods other than Rovin’s “best choice” have been used.

**Ignoring the Critics**

One potent response has been simply to ignore the critics. Sutton’s detailed criticisms of the classic fluoridation trials are not even mentioned in most discussions of the case for fluoridation. Likewise, Waldbott’s reports of toxic effects of fluoride are not referred to at all in many treatments.

Because the critics have been ignored, a number of technical disputes concerning the risks and benefits of fluoridation cannot be said to have been resolved scientifically. There has been no process of engagement with the arguments of the critics, allowing for a continual revision, refinement, and testing of claims. Often the antifluoridation material is simply assumed to be wrong or irrelevant and not worth refuting, and then just ignored. In other cases there is a response at first, as in the initial reviews of Sutton’s 1959 monograph, but no follow-through. Sutton’s second edition of 1960, including replies to his critics, was ignored.

This type of response can be successful only when the overwhelming weight of professional credibility and endorsement is on one side. If the critics are ignored, this seems to say that their views are not worth bothering with.

So far as most profluoridationists are concerned, the issues are closed and dead and not worth raising again. Antifluoridationists prefer a different interpretation. For them, the proponents ignore criticisms because a thorough examination of them might support the claims of the critics. If the opponents can persuade people that this is the real explanation for proponents’ silence, then ignoring the critics can be counterproductive.
Attacking in General Terms

A related approach is to attack the antifluoridationists in general terms, without mentioning any names or sources. For example, Dr. Russell B. Scobie, a pediatrician who "helped pioneer the drive in 1944 to have Newburgh selected for the now classic Newburgh-Kingston Fluoridation Study" and who has given lectures around the world on fluoridation, wrote "the opposition rely on innuendo, half-truths and deliberate untruths to support their position. They never ask for information, although they are always willing to provide instruction. They know the answer with a religious fervor and they are obviously not susceptible to educational efforts." Donald R. McNeil, in a 1969 booklet, Fluoridation: For Your Community and Your State, published by the ADA on how to promote fluoridation, described some of the arguments of the opponents but gave no names or references. He said, "Despite thousands of scientific studies on fluoridation and nearly unanimous agreement by scientists that it is safe, effective and worthwhile, fluoridation remains under attack. Few scientifically proven public health measures have been the object of such falsehood, distortion and deceit." Dental researcher Herschel Horowitz, a leading proponent in the United States, wrote in a mostly technical paper in the British Dental Journal that "It is truly unfortunate that a public health measure with these impressive attributes, on occasion, generates so much public controversy." Horowitz gave no reference to scientists among the critics of fluoridation.

Ronald J. Hunt, in an article about fluoridation in small Iowa towns, referred to the arguments of the opponents in only a couple of sentences: "opponents of the measure have found that it is much easier to create confusion and fear than it is to educate people. The fluoridation issue increases in complexity when antifluoridationists cause controversy by continuing to claim that fluoridation causes cancer and has been linked to other diseases, even though these claims have repeatedly been scientifically refuted." Hunt gave no references to scientific work on either side of the controversy.

A book called Appropriate Use of Fluorides for Human Health, published by the World Health Organization in 1986 and edited by J. J. Murray, a leading proponent of fluoridation, includes discussions of implementation of fluoridation, safety, legal aspects, and referendums, plus a mention of “the often misguided opposition to community fluoridation programmes," without giving a single reference to scientific criticisms.

A variant of this technique is found in a compilation called Classification and Appraisal of Objections to Fluoridation by Kenneth R. Elwell and Kenneth A. Easlick. More than 100 separate objections are listed, followed by responses including numerous references. What is evident on inspection is that, whereas the profluoridation arguments are well documented, the objections are not. The names of people making the objections are seldom mentioned, and their publications are seldom cited. The names of people making the objections are seldom mentioned, and their publications are seldom cited. For example, Alfred Taylor’s research on fluoride and cancer in mice is mentioned, but his publications on this topic are not cited, whereas responses to Taylor’s work are cited. Waldbott is not named but, instead, is alluded to as “a physician.” His publications are not cited.

Edward Groth III, after examining a wealth of scientific literature on fluoridation, concluded that virtually all sources “are tainted by detectable political bias.” He noted that the bias in antifluoridation reviews of the scientific literature is often overt, whereas in profluoridation sources it can be less obvious. In the latter, “Reports of the effectiveness and safety of fluoridation are extensively discussed, but the numerous studies which have suggested contradictory conclusions, or which contain critiques of the validity of the evidence presented, are often neither quoted nor listed in the bibliography. Such reports may mention allegations of harm from fluoridated water, and attempt to refute such allegations; but in doing so, the specific evidence that supports claims of potential harm is rarely discussed."
Scientific knowledge in controversy

This method of not giving the opponents the status of a name or an argument has been used frequently — for example, in numerous editorials and notices in the Journal of the American Dental Association over the years. Attacking the other side in unspecific terms can be done by anyone from any position, but it is especially useful for those who have more status, since they avoid giving recognition to the other side.

Circulating Unpublished Critiques

Another technique for attacking credibility is the unpublished critique. For example, after Mark Diesendorf’s Nature paper was published, a critique was written by Australian proponent Graham Craig and circulated to government health departments and editors of newspapers and journals. (Diesendorf eventually obtained a copy.) Craig’s critique was not designed to be published. In fact, in a cover letter to the editor of Nature, Craig stated that his letter and critique were not for publication. This technique avoids putting the criticisms in the open scientific literature where they can, in turn, be criticized. Hence this denies the criticized paper the status of being taken seriously in a prestigious open forum, but profluoridationists are able to use the unpublished critique when preparing responses for local debates.

Diesendorf found it difficult to respond to this. He prepared a reply, but it seems unusual to publish in a journal a response to unpublished material. But there was no obvious way to circulate his reply — or even notice of its existence — to all those who would have received the unpublished critique.

Another critique of Diesendorf’s Nature paper, by leading British proponents Murray and Andrew Rugg-Gunn, was “issued” by the British Fluoridation Society. Again, as the critique did not appear in the open scientific literature, Diesendorf had the same problems in replying.

Colquhoun has encountered similar difficulties. After the appearance of his two-part article in American Laboratory, a letter criticizing his research was circulated by the director of the Division of Dental Health’s head office in Wellington, New Zealand. The letter was written by Peter Hunter, principal dental officer for research. It alleged mistakes in Colquhoun’s calculations of decay rates in New Zealand school children. The letter was the basis for a statement circulated to local water supply authorities in New Zealand from the Director-General of Health, stating that Colquhoun’s data contained a serious error in at least one instance. Later, the Centers for Disease Control, part of the USPHS, reproduced the letter as part of one of their publications. At no time was Colquhoun sent a copy of the letter. When Colquhoun found out about the letter, he wrote to the Director-General of Health asking for access to the data to assess the alleged error, but this was denied.

An article by Colquhoun and Robert Mann criticizing the study of the effect of fluoridation in Hastings, New Zealand, appeared in the December 1986 issue of The Ecologist. The authors claimed that the Hastings results were wrong because the diagnostic criteria for tooth decay were changed in Hastings but not in the control town Napier. In 1988, they obtained by indirect means an unpublished critique of their paper by Peter Hunter and Elsdon Storey. This critique had been circulated to the general manager of the City of Hastings, among others, but not directly to Colquhoun and Mann. They responded by circulating a booklet reprinting the Hunter-Storey critique accompanied by comments of their own in reply.

The unpublished critique seems to be a common way to attack the credibility of opponents. For example, Ionel Rapaport’s studies of the link between fluoridation and mongoloid births were the subject of a critique by A. L. Russell, who did research supposedly refuting Rapaport. Russell’s research has never been published, but a letter of Russell’s about this research has been widely cited by profluoridationists.

Edward Groth III’s 1973 doctoral dissertation was seen as critical of fluoridation by many proponents. Leading proponent Ernest
Newbrun wrote an attack on the dissertation which was circulated by the USPHS for years. Groth did not learn of its existence for about ten years.

In one sense, the unpublished critique is a curious tactic, as the proponents undoubtedly have greater opportunities for publishing in dental journals. The advantage of the unpublished critique is that nothing about the issue being contested appears in dental journals at all, and so the issues are not raised to the status of being worthy of professional debate.

Prestigious dental journals generally do not publish antifluoridation articles. Nor do they often publish careful refutations of antifluoridation scientific work. Thus the antifluoridation scientists are not given recognition — not even the negative recognition of criticism — in the crucial journals. Responses remain in the domain of unpublished, informally circulated manuscripts.

This point was articulated well by leading proponent David B. Ast at the 1951 conference of dental directors where Francis Bull spoke. In commenting on how to respond to an “alleged rumor” about fluoridation and cancer, Ast said:

If a refutation is published it will reach a very much larger number of persons. I wonder if it would not be preferable for a refutation to be prepared at the University of Texas and made available to those who make inquiry for it, and for the dental directors to write to the University of Texas for that information. So if the question comes up in their community they will be well heeled with information to answer the question rather than to publicize this rumored information.

In exceptional cases, the work of opponents has sufficient impact to lead to refutations being published in scientific and dental journals. The claims of Yiamouyiannis and Burk on fluoridation and cancer stimulated replies by several scientists in medical and scientific journals. More recently, the studies by Diesendorf and Colquhoun in nondental journals, such as Nature and American Laboratory, have triggered proponents to write refutations in the Journal of Public Health Dentistry and the New Zealand Dental Journal.

To me, the most reasonable explanation for why critiques are sometimes published and sometimes not published is campaigning effectiveness. As long as the research critical of fluoridation is not widely known, it is more effective to circulate unpublished critiques. But when the research gains widespread publicity, publication of critiques may be warranted.

Claims about fluoridation and cancer were made by Alfred Taylor in 1950s and by Yiamouyiannis and Burk in the 1970s. It is hard to argue that differences in scientific quality explain the differences in the form of the responses to their work. The key is that Yiamouyiannis and Burk obtained enormous publicity for their work; Taylor did not. Hence, Taylor could be dealt with by an unpublished critique, whereas Yiamouyiannis and Burk merited published refutations. Similarly, the initial responses to Colquhoun and Diesendorf were unpublished critiques, but, as their work continued to attract considerable attention, published responses were deemed warranted.

This is not to say there is any conscious conspiracy to choose either publication or circulation of unpublished critiques. Rather, the struggle for credibility within the fluoridation controversy sets the general context in which the standing of various arguments and critics is assessed. Within this context, it then seems natural to choose a response that is more effective in the circumstances.

Attacking the Critics Personally

Yet another response to critics has been to attack them personally, rather than merely attacking their arguments. The aim here is to destroy personal credibility and authority.

In my interviews with fluoridation partisans, the scientific credibility of those on the other side was a key point in many comments. There were a number of statements under-
mining the status of those on the other side as scientific or scholarly. For example, one proponent told me that Geoffrey Smith was unable to get anything published in refereed scholarly journals, and could publish only via the unrefereed letters column of the *New Zealand Dental Journal*. (Smith told another story. Unable to get past the referees in the *Australian Dental Journal*, he had had no trouble getting his articles published in international scientific journals. He sent me reprints of several such articles.)

One proponent told me that Mark Diesendorf’s article in the prestigious scientific journal *Nature* had not been refereed, and that this information had come to him via a contact in Britain. According to Diesendorf, the article was refereed. He sent me a copy of the referee’s report and his correspondence with the editor of *Nature*.

The point here is that attempts were made to undermine the conventional scientific achievements of those on the other side. This was something that could be done more effectively by the proponents, since they have a near-monopoly over professional opinion and membership of key policy-making and advisory bodies.

A number of interviewees, both proponents and opponents, spontaneously mentioned the Briggs case. Michael Briggs had been a professor of human biology and dean of science at Deakin University in Geelong, not far from Melbourne. Allegations were raised in the early 1980s that Briggs had fabricated some of his research findings on oral contraceptives. Briggs denied any wrongdoing. In a drawn-out affair, the university had difficulties in initiating a formal inquiry into the allegations.

Eventually, Briggs resigned, and, not long afterward, died in Spain in 1986. A university investigation later concluded that data in at least some of Briggs’ publications was partly fabricated. The continued publicity about the Briggs case made his name a symbol of fraud in Australian science.

The way in which the Briggs case was mentioned by several proponents and opponents suggested that scientists on the other side could well be fraudulent. For example, one proponent noted, in relation to Diesendorf’s antifluoridation article in *Nature*, that Briggs had published in *Nature*. The implication was that even fraudulent work could get into prestigious journals, and so the publication of an antifluoridation paper there did not mean it was scientific.

Some proponents and opponents interviewed made highly derogatory comments about each other, but only about those on the other side. Some or all of those on the other side were called “unscientific,” “discredited,” and occasionally much stronger things such as “liars” and “fools.” Some very specific examples were offered to justify this sort of language. (Only some interviewees made such derogatory characterizations. They arose spontaneously in the interviews.)

Scientists — including leading scientists — commonly make derogatory and abusive comments about those with differing views, as is recognized by most people in the profession. It is less common for such attacks to be made in print. The fluoridation controversy is somewhat unusual in that the professional literature contains quite a number of personal attacks.

The Attack on Sutton. Donald Galagan’s 1960 review of Philip Sutton’s book contains some technical points, but also some personal attacks, including the following:

Although it is nothing new to see an accredited scientist mix fact and fancy, near truth with truth, and emotion with reason, it is always shocking to realise that an intelligent individual in a responsible position can so baldly misinterpret scientific data. … The contents of the monograph, therefore, represent no more than an exercise in semantic and scientific dilettantism designed to serve some other purpose. … I can only conclude that Dr Sutton has an intense and emotional drive to oppose fluoridation. Why he feels this way is not clear, but it seems likely to come from some motive other than a sincere concern
Struggle over credibility

There are several implications within these statements. Galagan accused Sutton of mixing "emotion with reason." The underlying assumption is that scientists should be concerned only with reason, and that emotion should not influence their judgments.

Galagan stated that Sutton was a dilettante or, in other words, not a "real" or professional scientist so far as this subject is concerned. Finally, Galagan concluded that Sutton was motivated to oppose fluoridation—with "motivated" suggesting some impulse other than truth or human welfare.

All of these implications serve to paint Sutton as other than scientific. The usual image of scientists is that they are rational, professional, and unmotivated by anything other than the search for truth. Galagan suggested that Sutton, in this piece of work, had not performed according to this scientific ideal.

This sort of attack shows again how the promoters of fluoridation have taken on the mantle of scientific orthodoxy. In the 1940s, it was the proponents who were political, emotional, and "motivated." John Frisch, according to McNeil, was "a man possessed" in his promotion of fluoridation: "Fluoridation became practically a religion with him." Even after the endorsements, proponents were often evangelistic in their activities. The difference is that, because they were then backed by professional authorities, their promotional activities were taken as compatible with scientific objectivity.

Actually, there are no statements in Sutton’s 1959 book suggesting emotionality or ulterior motivations. Sutton’s language and style is dry and characteristic of formal scientific writing. Ironically, it is Galagan’s review that contains emotional language — namely, his attacks on Sutton.

There is no paradox here. Galagan had assumed that Sutton was mixing reason with emotion precisely because Sutton was not wholeheartedly supporting fluoridation. Galagan had assumed that being critical of fluoridation is, itself, evidence of emotion and ulterior motives, whereas support for fluoridation is automatically rational and without ulterior motives.

The strategy implicit in Galagan’s attack on Sutton — namely to categorize any opposition to fluoridation as irrational by that very fact — has been openly pursued by proponents of fluoridation. Because right-wing and other fringe groups were vocal opponents of fluoridation in early years in the United States, it was an obvious strategy to respond by denigrating the credentials of the opponents rather than their arguments. The next stage of this strategy was to include anyone who was prominent in opposing fluoridation in the same basket. This is the familiar process of “guilt by association.”

The ADA Dossier. This process is most public in a dossier on opponents compiled by the Bureau of Public Information of the ADA since the mid 1950s. Versions were published in the Journal of the American Dental Association in 1962 and 1965. Entitled “Comments on the Opponents of Fluoridation,” the compilation begins, “The following pages contain excerpts from material concerning some of the individuals, organizations and publications opposed to the fluoridation of community water supplies. This material has been compiled for the general information of members of the dental profession and others interested in this public health measure.”

Many groups and individuals are listed, including right-wing groups, such as the John Birch Society and the Ku Klux Klan. The actual “comments” on these groups are almost entirely quotes from newspaper articles, journals, and letters. A large number of the quotes serve to classify the group or individual concerned as a “crank” or “quack.” For example, Dr. Morris A. Bealle, who edited a newsletter called American Capsule News, is said to be opposed to the Salk vaccine and to claim that polio comes from consuming soft drinks and ice cream, which occurs more often during hot weather.
Others on the list are documented as having been patients in mental hospitals or convicted for criminal activity, such as practicing medicine without a license. The Ku Klux Klan is included, seemingly only to show that it opposes fluoridation. For example, the *Chicago Sun-Times* of 22 May 1961 is quoted as saying that Klan leader Robert M. Shelton “has been actively opposed to increased state appropriations for mental health and against fluoridation of drinking water, contending they have subversive aims.”

On the other hand, some of the information is not particularly damning in and of itself. For example, the only information on Ludwik Gross is taken from a memorandum of 24 September 1962 by the Division of Dental Public Health and Resources of the USPHS.

Dr. Ludwik Gross, Chief of Cancer Research, for the Veterans Administration, states: “The plain fact that fluorine is an insidious poison, harmful, toxic and cumulative in its effect, even when injected in minimal amounts, will remain unchanged no matter how many times it will be repeated in print that fluoridation of the water supply is safe.” He also opposed fluoridation on the grounds that the consumption of water varies greatly, that the margin of safety is narrow and that the engineering problems in large cities are formidable. The Veteran’s Administration which employs Dr. Gross states: “Dr. Gross is free to offer his personal opinion in any relation he may desire. However, Dr. Gross does not speak for the Veteran’s Administration on the subject of fluoridation. This agency is not opposed to the fluoridation of public water supplies.”

Two points are worth noting. First, the USPHS went out of its way to deny that Gross spoke for anyone but himself. Second, the ADA saw fit to include this statement about Gross in its “Comments on the Opponents of Fluoridation.” By being included in a list with extreme right-wing groups, opponents of vaccination, other “health quacks,” and people with criminal convictions and admissions to mental hospitals, Gross’s opposition to fluoridation was implicitly categorized with these stigmatized groups.

**The Attack on Waldbott.** As mentioned before, George Waldbott was, for many years, the leading antifluoridation scientist in the United States. As an internationally respected allergist and author of numerous publications, Waldbott’s opposition to fluoridation was especially powerful. In addition, he was highly active in writing articles, giving talks, and presenting testimony against fluoridation. Any undermining of Waldbott’s credibility, therefore, would have been important for the cause of fluoridation.

The ADA’s dossier contains a large section on Waldbott. It begins with a statement by Dr. J. Roy Doty, secretary of the Council on Dental Therapeutics of the ADA, criticizing a circular by Waldbott on the grounds that Waldbott had not correctly reported certain items from the medical literature. This is clearly an attempt to impugn Waldbott’s claims to scientific status.

The second item is from a newspaper, the *Milwaukee Journal* of 8 November 1955. The item reports that Waldbott, as a witness against fluoridation, was challenged by Dr. E. R. Krumbiegel, the City of Milwaukee’s health commissioner. The *Journal* quoted Waldbott as saying that he was “the first person to describe allergic pneumonia as a disease,” and said that he was “the first to demonstrate the role of pollen in allergy.” Krumbiegel challenged this by stating that “a Dr. Loeffler” first described allergic pneumonia, and that the role of pollen in allergy had been demonstrated long before Waldbott grew up. Krumbiegel’s statements seem to show that Waldbott had made false claims concerning his own scientific discoveries, thus undermining his credibility on fluoridation as well.

The *Journal*’s article went on to quote several other witnesses critical of Waldbott. One was Francis Bull, who was quoted as saying “It’s astounding that we have to get a doctor from outside the state to tell us that people here are walking around half dead,”
and that people who opposed fluoridation were also opposed to nearly all public health measures.80

The Journal’s article also reported that Dr. Delbert P. Nachazel, identified as “chairman of the fluoridation committee of the dental association,” said that, after studying “all the available scientific reports on fluoridation,” he could find nothing written by Waldbott.81 His comments suggested that, if Waldbott had not published anything on fluoridation, his views were not worth that much.

These comments are highly damaging to Waldbott’s credibility as a scientist and, hence, as a critic of fluoridation. Waldbott was well aware of this, and wrote a letter to the ADA responding to a number of the claims. Unlike all other entries in the ADA dossier, the material on Waldbott includes a response by Waldbott. He wrote, “At no time have I stated that I was the first to discover the role of pollen in allergy as claimed. I stated that I was first to discover the role of pollen in chronic perennial asthma.” He also states that allergic pneumonia, which he first described, had nothing to do with “Loeffler’s Syndrome.” The ADA dossier also mentions that Waldbott, in another letter, said he had had “thirteen articles published in medical journals.”82

Much of the material on Waldbott in the ADA dossier serves to damage Waldbott’s credibility without responding to his arguments. Although Waldbott was able to reply to some of this in the published version of the dossier, material from the dossier was widely used in campaigning for fluoridation. A dossier on Waldbott was first issued by the ADA in 1955. Its effect is best described in his own words.

This dossier accused me of intellectual dishonesty and incompetence. I was grouped with lay opponents, one of whom was alleged to have escaped from a mental institution, the other was claimed to be an imposter. Subsequently, wherever I raised my voice against fluoridation, this dossier always showed up like a steady companion. It was made available by the American Dental Association through local dentists and by the U.S.P.H.S. through local health officials. It was sent to fluoridation committees of district dental societies. It was handed to newspaper editors, physicians, dentists, medical editors, officials of medical societies, key lay persons, leaders of clubs and organizations, wherever and whenever there was a need for countering my data. It reached the desks of the Svenska Dagbladet, Stockholm, Sweden; the Berner Bund, Switzerland; the New Zealand Fluoridation Commission. It showed up in Germany, in Holland and in hundreds of communities in the U.S.A. from Jacksonville, Florida, to Boston, Mass.; from New York City to Seattle, Washington. Rarely, if ever, was I aware where it had appeared until it was too late to reply to the allegations.83

Frank J. McClure was a leading USPHS researcher whose work supported the promotion of fluoridation in the United States. His book Water Fluoridation: The Search and the Victory, published in 1970, is a classic in the literature favoring fluoridation. In the final chapter, “Contest and Victory,” McClure gave his version of the fluoridation debate and included a section on Waldbott. McClure’s treatment of Waldbott is revealing in its focus on Waldbott’s personal behavior in the debate, rather than on the findings Waldbott reported in the medical literature.

McClure began by referring to the ADA dossier and mentioning some of the extremist groups opposed to fluoridation, naming the Ku Klux Klan, the John Birch Society, and the American Association for Medico-Physical Research. In the same paragraph he then discussed “two leading opponents of fluoridation,” George L. Waldbott and Frederick B. Exner.

Referring to Waldbott’s reports of fluoride poisoning from water fluoridation (citing Waldbott’s book, A Struggle with Titans, but not any of his numerous research papers published on the topic), McClure said “This threat has been the theme of most [of] the antifluoridationists’ efforts to discredit the findings of recognized scientists and health
organizations." McClure characterized Waldbott’s research as “threats,” and counterposed Waldbott’s findings with those of “recognized scientists and health organizations,” thus implying that Waldbott was not a “recognized scientist.”

McClure next referred to an instance in which the City of Milwaukee’s Health Department offered to test one of Waldbott’s “cases of fluoride poisoning” (McClure’s quotes) in a hospital. Waldbott declined. This suggests that Waldbott was afraid to let others replicate his clinical findings. This may well have been the case, but McClure did not mention that Waldbott might have had legitimate reasons to refuse.

McClure moves on to the visit to Waldbott by Dr. Heinrich Hornung, an “experienced public health officer” from Kassel-Wilhelmshoche, who was “dedicated to the promotion of dental health in Germany.” In a letter to the Journal of the American Dental Association, Hornung claimed that Waldbott had not personally investigated the cases of alleged poisoning caused by fluoridation. McClure quoted from Hornung’s letter, concluding with this statement: “The American Dental Association and the public health authorities are fully justified in their contention that Dr. Waldbott presented no proof to substantiate his belief that chronic poisoning had been caused by water fluoridation, and those organizations, therefore, should proceed with their program.”

This is an excellent example of how to discredit a scientist’s findings by exposing the human underside of published findings. Hornung’s visit to Waldbott allowed him to see Waldbott’s files and, later, to expose what he said was a lack of proper scientific investigation behind Waldbott’s published claims. McClure used Hornung’s statements to do the same.

Waldbott devoted several pages to the Hornung visit in his book A Struggle with Titans. Hornung, according to Waldbott, was “one of Europe’s most fanatical promoters” of fluoridation. Hornung came to the United States to study fluoridation, and made a stop at Waldbott’s clinic near Detroit. Waldbott showed him around his farm and showed him data about fifty-two “cases of poisoning from fluoridated water, a report of which was about to appear in a leading European medical journal, Acta Medica Scandinavica.”

According to Waldbott, he had sent a questionnaire to individuals to see which ones were worthy of investigating more carefully. Waldbott said he used the questionnaire to decide whether to contact the family physician, and that he personally examined most of the fifty-two people.

Later, Hornung sent a letter to fluoride pioneer Frederick McKay, with a copy to Waldbott. This letter was also published in the Journal of the American Dental Association. It is the letter quoted by McClure. In it, Hornung said that “Dr. Waldbott distributed a questionnaire in which ‘leading’ questions were listed, and whenever a single one of these questions was answered positively by one of the recipients of the questionnaire (mostly elderly ladies), this was recorded as proof of poisoning by fluoridation.”

Waldbott mentioned other distortions in Hornung’s letter, saying that Hornung “must have lifted out of context and attributed to me some of the patients’ own descriptions in their replies to my questionnaire.” Essentially, Hornung used access to Waldbott’s research files to discredit the research by exposing apparent inadequacies observable only to an insider.

As most researchers will admit, an examination of their day-to-day activities, including failed experiments, rejected hypotheses, and sloppiness, can give quite a different impression than their polished reports in scientific journals. Inside descriptions, even with the best intentions, can undermine claims to being objective and scholarly. With hostile aims, the results can be damning, indeed. To expose the limitations of the insider description, an alternative description of day-to-day procedures is usually required, and this can never appear to be as authoritative as a published account giving an idealized reconstruction of research procedures.

For Hornung to write about his observations to a dentist and researcher, Frederick McKay,
was one thing. For the account to be published in the central journal of the dental profession in the United States, the *Journal of the American Dental Association*, gave it much more visibility and credibility. The ADA made full use of the letter. According to Waldbott, it was the subject of a nationwide news release on 31 August 1956 and used heavily thereafter. He said, “The American Dental Association and the P.H.S. utilized this letter for all it was worth. ... Whenever my name was mentioned in connection with fluoridation, the local promoting dentist or health official handed the story to the newspaper or the local fluoridation committee.”

Waldbott clearly made a mistake in allowing Hornung access to his files. He commented, “the thought would never have crossed my mind that a health official’s motives could be political rather than scientific. His gift of roses to my wife had convinced me that he was a gentleman. It was perhaps my German background which made me assume that a scientist, a German, and a gentleman could only be interested in science and truth.”

Now, to return to McClure’s abbreviated account of Hornung’s encounter with Waldbott: after a brief resume and quotations from Hornung’s letter, McClure gave Waldbott’s side. “In *A Struggle with Titans* Waldbott accused Dr. Horning [sic] of quoting him erroneously in the letter to McKay.” McClure then turned to other comments on Waldbott and Exner. By giving no detail about Waldbott’s response to Hornung, McClure left the impression that Waldbott did no more than “accuse” Hornung of quoting him erroneously and without further substantiation.

McClure concluded his few paragraphs on Waldbott and Exner with these comments:

Neither of these men appears to have engaged personally in a constructive program of research on the dental or physiological effects of fluoridated water. Neither are dentists, and apparently have only limited interests in basic physiology and biochemistry, essential for clinical and epidemiological research. The charges of these physicians regarding health hazards of fluoridated water are lacking in substantial evidence and are rejected by the majority of physicians, scientists, and public health authorities.

McClure first accused Waldbott and Exner of not being engaged in a “constructive program of research.” Certainly, Waldbott was engaged on a program of research, but, presumably because he was opposed to fluoridation, this program was not considered to be “constructive” by McClure. The fact that Waldbott was not a dentist appears to be held against Waldbott, although the relevance of being a dentist to studying fluoride toxicity is not clear. McClure’s statement that claims by Waldbott and Exner on hazards of fluoridated water “are lacking in substantial evidence” sounds authoritative. It provides a striking contrast to McClure’s lack of analysis of any of Waldbott’s scientific papers and his concentration on criticisms of Waldbott’s behavior.

McClure concluded by saying that the charges by Waldbott and Exner were “rejected by the majority of physicians, scientists, and public health authorities.” This statement might suggest that this rejection was the result of scientific examination of the charges. The role of the ADA in promulgating Hornung’s attack is not mentioned, although arguably, this played a major role in the rejection of Waldbott’s work.

As noted in chapter 2, Waldbott’s research findings are seldom mentioned in recent reviews by fluoridation supporters. The campaign against Waldbott by the profluoridationists, as supported by the USPHS and the ADA, served to discredit Waldbott in the eyes of most dentists and doctors. Perhaps it is not surprising that few scientists have made serious attempts to find and study cases of fluoride toxicity.

The Attack on Yiamouyiannis. In the mid 1970s, biochemist John Yiamouyiannis argued that fluoridation was associated with increased cancer death rates, and quickly became a leading opponent of fluoridation. To argue a
A link between fluoridation and cancer is an especially potent challenge because cancer is symbolically a “dread disease,” perceived as an especially horrible way to die. The claims by Yiamouyiannis and his collaborator Dean Burk have been repeatedly challenged in scientific forums. But in addition, Burk and Yiamouyiannis have been personally attacked on numerous occasions.

Setting the tone for the attack was an unsigned article in the prestigious American consumer magazine *Consumer Reports* in July 1978, entitled “Fluoridation: The Cancer Scare.” This article is of unusual importance since it is widely known to dentists and doctors and often provides the basis for their response to the claims by Burk and Yiamouyiannis. The article opens with Burk’s appearance on Dutch television on 10 February 1976, an appearance the *Consumer Reports* author credits with the repeal of fluoridation in the Netherlands, previously the most highly fluoridated country in Europe.

The article gives a history of fluoridation, and then turns to the National Health Federation (NHF), which was set up in the mid-1950s by Fred J. Hart. Both Hart and the NHF were investigated by the federal Food and Drug Administration for making false medical claims. The FDA reported “From its inception, the federation has been a front for promoters of unproved remedies, eccentric theories and quackery.” Among its concerns, the Federation opposed fluoridation. According to *Consumer Reports*, “in 1974 the NHF decided to mount a new national campaign to ‘break the back’ of fluoridation efforts. It hired Dr. Yiamouyiannis to do the job.”

Yiamouyiannis did a study showing a positive correlation between fluoridation and cancer death rates in American cities. Setting a higher priority on campaigning than scientific publication, Yiamouyiannis first “published” his findings as a campaign leaflet for a referendum in Los Angeles. Only later did he seek publication in scientific journals. Nevertheless, it is interesting to note the response to Yiamouyiannis.

*Consumer Reports* quotes Thomas Mack, a Los Angeles doctor, commenting on Yiamouyiannis’s work: “All over the documents one finds … conclusions emblazoned essentially in the form of slogans, without cautious interpretation or restrictions … this bias is so pervasive and obvious, the mistaken logic so gross and naive, that the reader assumes the author to be, however competent in his Ph.D. field, totally unaware of the principles of epidemiology.”

*Consumer Reports* goes on to comment: “Most people are unfamiliar with the principles of epidemiology, however, and a Ph.D. degree can sometimes lend credibility even to claptrap. In Los Angeles it evidently did. The scare tactics of the NHF and other antifluoridationists scored a stunning victory over dental health.”

The article continues by describing the collaboration between Burk and Yiamouyiannis and their use of their findings to campaign against fluoridation in Britain and the United States.

The charges against Yiamouyiannis and Burk are fairly clear. Yiamouyiannis worked for an organization associated with medical quackery; their research was biased and uninformed, and was motivated by the aim of opposing fluoridation; and they have not published in the open scientific literature. These attacks are more effective against Yiamouyiannis, since he is the one who worked for the NHF. It is harder to attack Burk, a prominent biochemist who worked for the National Cancer Institute. *Consumer Reports* said “Like the National Health Federation, Dr. Burk is a leading advocate of the worthless cancer drug Laetrile … and he shares the NHF’s aversion to fluoridation.”

Burk is damned by his association with the causes of the NHF.

This same sort of guilt by association is used in a profluoridation article by Mary Bernhardt and Bob Sprague, entitled “The poisonmongers.” After introducing Yiamouyiannis as the most active opponent in the United States, they commented that “Yiamouyiannis is often accompanied by Dean Burk, Ph.D., another biochemist. Burk is
a retired employee of the National Cancer Institute, the highly respected branch of the U.S. Public Health Service which evaluates proposed cancer treatments to see if they work. But in recent years, Burk has been a major promoter of the worthless cancer remedy, laetrile.\textsuperscript{103}

The damning of Burk by association with laetrile is intriguing. Support for laetrile is taken by the defenders of medical orthodoxy as a sign of being “beyond the pale,” exactly as is opposition to fluoridation.\textsuperscript{104} Supporters of “unorthodox” cancer treatments have been denigrated in a fashion similar to the response to antifluoridationists.\textsuperscript{105}

Bernhardt and Sprague continue their discussion:

Yiamouyiannis and Burk claim that fluoridation causes cancer. But their claim is based upon a misinterpretation of certain government statistics. In true anti fashion, they compared cancer death rates in fluoridated and non-fluoridated cities. But they failed to consider various factors in each city (such as industrial pollution) which are known to raise the cancer death rate. When the National Cancer Institute did a genuine comparative study, it found no link between fluoridation and cancer. Undaunted, Yiamouyiannis and Burk charged NCI with a “cover-up.” They were joined in this hoax by Congressman James Delaney, who is an anti of long standing.\textsuperscript{106}

The most fascinating part of this quote is the implication that comparing cancer death rates in fluoridated and non-fluoridated cities is an “anti” way of studying the link between fluoridation and cancer. Bernhardt and Sprague suggest that being a “devout anti” is some sort of psychological problem. They say “It is important to realize that a devout anti cannot be dissuaded by facts,” and they refer to an article suggesting unconscious drives in many of those opposed to fluoridation.

Most damaging to the cause of fluoridation are the few antis who are physicians, dentists or others who presumably should be able to judge fluoridation on its merits. Some of them are simply misinformed. Others are alienated for reasons unconnected with fluoridation, but take this cause to get back at the scientific community which they feel has “slied” them.\textsuperscript{107}

Here, Bernhardt and Sprague spell out why opposition by scientists such as Yiamouyiannis and Burk is so important. Opponents who are not physicians, dentists, or scientists can be dismissed as ignorant of the facts. They do not fall into the category of those “who presumably should be able to judge fluoridation on its merits.” Hence, it becomes especially important to undermine the credibility of Yiamouyiannis, Burk, and any other credentialed individuals who become prominent in the opposition.

The Bernhardt-Sprague attack on antifluoridationists has been widely used by proponents. An example is Yiamouyiannis’s invitation to debate fluoridation in St. Charles, Missouri. Dr. Michael Garvey, a local dentist, was invited to present the case for fluoridation, but he refused to participate. Instead, he released a press statement, which included the following:

Yiamouyiannis is viewed in the bona fide scientific medical and dental community as a walking example of scientific fraud. The problem is, that he’s so smooth in his presentation that the average person without scientific background will be snowed and is likely to believe his every word. This Yiamouyiannis is a “poisonmonger,” according to experts in the bona fide scientific community.\textsuperscript{108}

Garvey’s view clearly is taken from the Bernhardt-Sprague article, which is entitled “The Poisonmongers,” a term referring to the opponents of fluoridation who spread “poison” into people’s minds. According to Bernhardt and Sprague:

The antis’ basic technique is the big lie. Made infamous by Hitler, it is simple to use, yet surprisingly effective. It consists of
claiming that fluoridation causes cancer, heart disease, kidney disease and other serious ailments which people fear. The fact that there is no supporting evidence for such claims does not matter. The trick is to keep repeating them — because if something is said often enough, people tend to think there must be some truth to it.109

Antifluoridationists find this sort of attack especially annoying, since, in their view, fluoride is the poison. One way they could respond is to point out that neither of the authors of this article is a qualified expert in the field. Both Mary Bernhardt and Bob Sprague are listed as freelance journalists. Bernhardt was also secretary of the Council on Dental Health of the American Dental Association from 1968 to 1976.110

As noted earlier, there was also a serious scientific response to the work of Yiamouyiannis and Burk, even though their work was not published in high-status scientific journals. As I argued before, this phenomenon is best explained by the political effectiveness of their claims. Richard Doll and Leo Kinlen, who did one of the studies challenging Yiamouyiannis and Burk, commented that “The preparation of our paper was prompted by the concern aroused at the wide publicity that Burk and Yiamouyiannis had sought and obtained in Britain for their misleading use of crude cancer-mortality rates in fluoridated and non-fluoridated U.S. cities.”111 But the scientific response was not treated as sufficient. There was a concerted attack on the credibility of Yiamouyiannis as a person as well.

More than one can play the game of attacking the credentials, motivations, and honesty of those with opposite views. But the proponents have won this battle over reputation in an overwhelming fashion because they have the preponderance of professional support and especially the backing of professional societies and many ardent supporters who are willing to use their resources to the utmost.112

**CONCLUSION**

In chapter 2, I described the main arguments used in the struggle over fluoridation, presenting them as a form of intellectual struggle. But the “debate” has been more than intellectual. It has been a highly polarized confrontation in which evidence and arguments are deployed to win adherents, both expert and nonexpert. The polarization of debate helps to explain the remarkable coherency of views of fluoridation partisans, who regularly line up in opposition on every issue, as described in chapter 3. Thus, in order to understand the deployment of arguments, it is necessary to place them in the wider context of polarized confrontation.

In this chapter I have described how the partisans seek not just to destroy the arguments of those on the other side, but also to minimize or destroy their personal credibility by citing endorsements, refusing to debate, making derogatory personal comments, and implying guilt by association with unsavory individuals and stigmatized groups. This form of attack has been most successfully used by the proponents against the opponents, mainly because the proponents have had a near-monopoly over authoritative backing and the professional resources to undertake this style of struggle. The opponents, by contrast, have had insufficient professional authority or control over professional resources to launch a similarly effective attack on the proponents.

In this aspect of the struggle, scientific and nonscientific aspects of credibility and authority are intertwined. It was precisely because Waldbott both had a reputation as a scientist and was heavily involved in campaigning against fluoridation that he was a prime target for attacks on his credibility.

An evaluation of the scientific aspects of the fluoridation issue is impossible without an assessment of the impact of the various techniques used to highlight or downplay certain scientific findings and to bolster or denigrate the reputations of the scientists presenting them. The struggle over credibility is a key to understanding both the acceptance or rejection of claims of scientific knowledge.
and the use of science as a tool in the power struggle over fluoridation.

NOTES

2. Ibid., 61-62.
4. Ibid., 249-255.
17. Ibid., 140. This view has much support among proponents. See, for example, Donald R. McNeil, “Time to Walk Boldly,” Journal of the American Dental Association, vol. 63, no. 3 (September 1961): 333-343.
20. Raulet, op. cit. Donald R. McNeil, in Fluoridation: For Your Community and Your
State, American Dental Association (1969): 16, describes the problem from the point of view of proponents. “As for debates, the question of whether to debate a scientifically proven measure such as fluoridation has plagued citizens’ committees for years. Experience has shown that only if proper ground rules are established should a citizens’ committee agree to debate. Too many debates degenerate into wide-open affairs surrounded by a carnival atmosphere, with intelligent reason falling by the wayside.”


22. For example, Exner and Waldbott, op. cit., 148-149, 177-178. For a proponent’s assessment, see McNeil (1961), op. cit.


24. Waldbott et al., op. cit., 264-265. Waldbott is wrong on this last statement, according to Brian Burt, who says the experience of dental researchers is that very mildly mottled teeth do not get worse over time.


26. Ibid., 11.

27. Ibid., 12.

28. Ibid.

29. Ibid., 17.


31. Ibid., 358.


33. Exner and Waldbott, op. cit., 126.

34. Ibid., 118.

35. Ibid., 119.


37. Ibid., 3.


41. Ibid.

42. A few proponents, such as Donald R. Taves, have treated the opponents’ arguments more seriously. See Edward Groth III’s comments on reviews of the scientific literature in his commentary in this book.

43. I thank Edward Groth III for useful comments on this point.


Their response to Waldott relies heavily on the Hornung episode, described later in this chapter.


57. Frederick J. Scott, Jr., “Fluoridation Won’t Rest in Peace or Turmoil,” *American Laboratory* (September 1986): 8, 10.


60. Groth, op. cit., 295.


62. See the next chapter. One dental journal that has published a number of antifluoridation articles is the *Pakistan Dental Review*, hardly a prestigious publication.


64. See chapter 2, note 41.


67. One curious consequence of this is that the published responses may make use of the unpublished critiques, as in Burt and Beltran’s (op. cit., 214) use of Graham Craig’s
unpublished critique of Diesendorf’s *Nature* paper.


71. Groth (1973), op. cit.: 172-177, gives examples on both sides.


73. McNeil (1957), op. cit.: 50.


76. Ibid., 701, 1172.

77. Ibid., 1171.

78. Ibid., 708-709 and 1180-1181.

79. Ibid., 709, 1181.

80. Ibid., 710, 1182.

81. Ibid.

82. Ibid., 710, 1182 (emphasis in the original). Waldbott responded to an earlier, unpublished version of the dossier in George L. Waldbott, letter, *Journal of the American Dental Association*, vol. 55, no. 6 (December 1957): 873.


84. McClure, op. cit., 264.

85. Ibid.

86. Ibid., 265; the original is Heinrich Hornung, “Fluoridation: Observations of a German Professor and Public Health Officer,” *Journal of the American Dental Association*, vol. 53, no. 3 (September 1956): 325-326, at 326.

87. Waldbott (1965), op. cit.: 229.


89. Waldbott (1965), op. cit.: 231.

90. Ibid., 232.

91. Ibid.


93. Ibid.
94. See also Groth (1973), op. cit., 310-321, for an account of the treatment of Waldbott.


97. Consumer Reports, op. cit., 394.

98. Ibid., 395. This passage has been quoted frequently in proponent literature.

99. I thank Edward Groth III for this information.

100. Consumer Reports, op. cit., 395.

101. Ibid.

102. Ibid.


106. Berhardt and Sprague, op. cit., 219 (emphasis in the original).

107. Ibid., 217.


109. Bernhardt and Sprague, op. cit., 212 (emphasis in the original).


112. The treatment of scientists such as Alfred Taylor, who did studies on fluoride and cancer in mice, and Ionel Rapaport, who examined links between fluoridation and mongoloid births, illustrates all the points made in this chapter. See the excellent account in Groth (1973), op. cit.: 279-296.
Professional attack

What I have called in the previous chapter the “struggle over credibility” has mainly been carried out using rhetoric, namely written and spoken language. In spite of the viciousness of some of the verbal attacks, language has its limits. By itself, rhetoric does not have the capacity to prevent a scientist from doing research nor does it bar a dentist from dental practice.

Rhetoric is a way of exercising power, but there are other ways. In the fluoridation controversy, methods of struggle have not been limited to rhetoric. In this chapter, I present a number of cases in which attempts have been made to stop antifluoridationists from expressing their views, doing research, and practicing dentistry.1

The implication of these examples is that the fluoridation debate has used more than rhetorical tools. Various other forms of power have been deployed. It is necessary to realize the extent of this activity in order to understand the dynamics of the fluoridation issue. In particular, assessing the technical disputes over fluoridation requires a simultaneous assessment of the wider exercise of power.

Most of the cases of the sort presented here have been documented by antifluoridationists. Some may be incorrect or overstated. But the number of cases is very large, and they fall into comprehensible patterns. In my study of this phenomenon in other areas, there are always many more cases occurring than end up being documented.2 I am convinced that these cases point to an important dynamic in the fluoridation controversy. What the cases actually mean is something to which I will return to later in this chapter.

SOME CASES

Dr. John Neilands, professor of biochemistry at the University of California at Berkeley, signed a ballot argument against fluoridation. A local proponent of fluoridation wrote to the chancellor of the university requesting that Neilands be reprimanded, and called for him to be expelled from his professional society.3

Ivan H. Northfield, a dentist living in Duluth, Minnesota, made a speech against fluoridation during a campaign in 1965. As a result, his local dental society suspended his membership for one year, without allowing him to speak in his own defense.4

In 1964, a sociology student at a U.S. university carried out a survey of a medical society and found that only half of the respondents favored fluoridation while a third opposed it. George Waldbott reports that “The assistant dean, prompted by the fluoridation chairman, wrote a letter berating the student for allegedly abusing the good name of her school.” Although threat of a legal action by the student forced a retraction of the letter’s allegations, the attack discouraged the student from publishing her data.5

While Edward Groth III was a graduate student in biology at Stanford University in the late 1960s, he became interested in the fluoridation issue and, after studying the arguments, wrote a letter to the president of the university suggesting that a ballot argument for the proponents had falsely claimed that there was no evidence of harm. Groth sent copies of his letter to two proponents whom he had interviewed. One of them approached the head of the biology department and vehemently attacked Groth at length, suggesting that he should be expelled from graduate school. But the department head defended Groth.6

Dr. Chong W. Chang had done work showing that fluoride interfered with the biochemistry of living tissues. Chang said in a 1972 letter to Waldbott “I have been associated with six years of basic research on fluoride since my study at the University of California and the USDA [U.S. Department of
Agriculture] here. However, in recent years, USDA keep demanding me to do the research area which is not related to fluoride. After careful consideration, I have strongly determined to find some other position where I could continue my research on fluoride.

Virginia Crawford, a registered nurse living in Detroit, found that she was severely affected by fluoridated water, and became a vocal opponent. In 1964, she stated that many people had threatened that her nursing license would be taken away because of her activities.

According to George Waldbott, in the 1950s “one internist, still practicing in Detroit, received a warning from a member of his hospital staff. Should he continue to publicly oppose fluoridation he would jeopardize his consultant practice, even his hospital staff appointment. He was profoundly distressed. Reluctantly he withdrew. He had no other choice.”

A doctor in Windsor, Ontario who recommended in 1962 to a patient to stop drinking fluoridated water in order to overcome a stomach ailment asked the patient to refrain from revealing his diagnosis to anyone so that his position in the eyes of colleagues, especially Windsor’s medical officer for health, would not be jeopardized.

Waldbott also described a case of misrepresentation in 1965, in which prominent profluoridationists presented themselves as antifluoridationists to a woman whose doctor had advised her to avoid fluoridated water in order to overcome health problems. After she revealed the name of her physician, five profluoridationists visited him. “After their visit he had no choice but to remain silent.”

A letter from an independent fluoridation promotion group, the Committee for the Betterment of Oral Health, based in Allentown, Pennsylvania, stated in 1961 that “We now have spies in most of the established national organizations opposed to fluoridation and can now anticipate the moves they are making and we can really hit hard now, of course, this is not for publication.”

Waldbott said that, whereas many presidents or secretaries of dental or medical societies would privately express concern about fluoridation, to do so openly would mean the end of their careers in these societies.

Carol Farkas, a Canadian researcher who has studied the levels of fluoride in foods and warned that some people may be ingesting too much fluoride, gave a talk on this subject to the Canadian Dental Association’s annual meeting in the 1970s. After the talk, several dentists came forward, asked for her phone number and said they would call. Five of them did so, “saying they agreed with what I had said but couldn’t say so in public because they would get black-balled from the CDA.”

In 1963, Dr. R. J. Berry of Oxford published results of research showing a reduction in the rate of growth of cancer cells in the presence of 0.1 parts per million of fluoride. This sounded good in terms of cancer, but actually pointed to the dangers of fluoride for normal cells. At any rate, Berry decided to abandon further work on fluoride after being criticized and subjected to “veiled threats.”

Hans Moolenburgh, a doctor and leader of the campaign against fluoridation in the Netherlands, reports that he was instructed by a medical official not to write articles against fluoridation. A friend of Moolenburgh’s, named Mien Bulthuis, did research for her dissertation on the role of fluoride in inhibiting the activity of the enzyme cholinesterase. A special committee of the Netherlands’ Health Board discussed the dissertation in May 1973. According to the minutes of the meeting, “Mr de Wael remarks [that] he has had a telephone call from Mr Drion (Chief Inspector of Health), who requested that he exert his influence in order to prevent remarks relating to the possible effect of fluoride on humanity from being published in the Bulthuis dissertation, as the subject was already receiving so much publicity that it could cause unrest among the population.”

John Polya, associate professor of chemistry at the University of Tasmania, claimed in 1973 that his staff and equipment had been taken away because of his public opposition to fluoridation.

Geoffrey Smith in 1979 worked as a dentist at Proserpine Hospital in Queensland and
supervised a dental therapist at a local primary school. He drew attention to the high level of dental fluorosis in children there, and began collecting data on this and on dietary sources of fluoride. He claims he was officially warned by the Queensland Health Department to cease the research and, after media coverage elsewhere in the country, was fired.21

Mark Diesendorf worked until 1985 as a principal research scientist at the Commonwealth Scientific and Industrial Research Organization (CSIRO). Officials of the Australian Dental Association wrote letters to the chairman of CSIRO and to the federal Minister for Science and Technology, who was responsible for CSIRO, complaining, for example, that Diesendorf had “mis-used his CSIRO connections to lend weight to his views on subjects outside his expertise,” and requesting the taking of “all necessary steps to ensure [that] this deceptive practice does not continue.” CSIRO defended Diesendorf in correspondence on the grounds that he had made clear that he spoke about fluoridation in his “private capacity.”22

In 1986, Mark Donohoe, a doctor, wrote a letter to the editor of a regional Australian newspaper, attacking fluoridation. He received a letter from the state medical board informing him that the board had received a complaint about his letter to the editor, that the board had concern that his comments were not in agreement with standard medical views, and that a newspaper was not the most appropriate place to present his views on fluoridation.23

This is an example of what Waldbott would call a “veiled threat.”

John Colquhoun describes the difficulty of assessing the role of pressure against antifluoridationists in the following manner.

In New Zealand the late R E T Hewat resigned from his position with the Medical Research Council in the same year that he revealed to his colleagues his doubts about the paradigm. The author knows that he was fulfilling a long-held wish to go farming, but to what extent he was influenced by pressures to make his decision at that particular time, with the Hastings experi-

Colquhoun himself experienced direct pressure. After being quoted, in a newspaper article, as warning parents about the danger of their preschool children swallowing fluoride toothpaste, he received a letter from his employer, the Director-General of the New Zealand Health Department. The letter stated that “a staff member who is required to carry out instructions which are abhorrent to him should seek a transfer to another position where this conflict will not exist, or he should resign.”25

A colleague of Colquhoun’s who made a similar warning in a newspaper, but anonymously, “was visited by a superior officer who had learned her identity and warned that she had committed ‘a dismissible offence’” since she, like Colquhoun, had contradicted the official policy that recommended fluoride toothpaste for all children with teeth, namely older than two and a half.26

In New Zealand in the 1950s, profluoridationists even arranged
for the police to secretly investigate the political affiliations of opponents.\textsuperscript{27}

The combination of direct attacks on some public opponents of fluoridation, their fears about loss of grants, and the general labeling of opponents as ignorant and misguided combine to discourage many scientists from doing research or speaking out on the issues. The relative lack of open opposition, in turn, encourages a perception of the “fringe” position of critics.

The direct attacks that occur, plus fears of jeopardizing careers, help to ensure that research projects that may lead to criticism of fluoridation are less often undertaken, and create an atmosphere in which those studies that are carried out are affected by a profluoridation bias.\textsuperscript{28} Hence, relatively few articles critical of fluoridation are ever submitted to scholarly journals. Of those that are, there is evidence that it is more than usually difficult to obtain publication.

Mark Diesendorf submitted an article critical of fluoridation to the Australian journal \textit{New Doctor}. It was rejected because “it might encourage the antifluoridationists.” The editor did not supply the referee’s comments, and would not even write in a letter that the article was rejected. He offered this information only over the telephone.\textsuperscript{29}

Sohan L. Manocha, Harold Warner, and Zbigniew L. Olkowski submitted a paper about enzyme changes in monkeys who drank fluoridated water to the \textit{Journal of Environmental Health}. One reviewer wrote that the paper “appears to be written with the intent to discredit the use of fluoridated water for the maintenance of dental health” and wondered, since the safety of fluoridated water had been demonstrated “exhaustively and repeatedly,” whether there was any point in “reviving an issue that has already been resolved.” Another reviewer gave, as a reason for recommending against publication, this statement: “this is a sensitive subject and any publication in this area is subject to interpretation by anti-fluoridation groups. Therefore, any detrimental fluoride effect has to be conclusively proven.” The paper was rejected. The authors were warned by their head of department not to seek publication in any other U.S. journal, since the head had been cautioned by the National Institute of Dental Research that the results would hurt the fluoridation cause.\textsuperscript{30}

British scientist R. S. Scorer wrote, “I know of one paper rejected by a prestigious British journal on the grounds that it would cause public alarm if published — it raised the issue of a possible relationship between fluoride and cancer mortality.”\textsuperscript{31}

Waldbott, in a court hearing, was asked, “How did it happen that the \textit{Journal of the American Medical Association}, the \textit{Annals of Internal Medicine}, the \textit{Journal of Gerontology}, and \textit{Annals of Allergy} turned down your articles on fluoride poisoning?” Since the question enumerated “every single journal that had ever rejected an article of mine,” Waldbott inferred that Public Health Service officials, as editorial consultants, must have advised the editors of these journals to turn down the articles, and that the editors had provided the information that they had done so.\textsuperscript{32}

Albert Schatz, often noted as the co-discoverer of streptomycin, sent three separate letters to the editor of the \textit{Journal of the American Dental Association} in the 1960s. Apparently because Schatz was a known critic of fluoridation, all three certified letters were refused and returned to Schatz unopened.\textsuperscript{33}

On 15-17 October 1962, a conference on the toxicology of fluorine was held in Bern, Switzerland. The conference was originally planned for the Netherlands but, due to “opposition from dental interests” there, it was transferred to Bern. The conference proceedings were to be published as a book. One publisher of medical and dental literature set the text in type, investing some 10,000 Swiss francs, before pulling out. The publisher was allegedly threatened by a boycott from the dental profession, and was offered compensation for dropping the book.\textsuperscript{34}

Philip Sutton reports that after the first edition of his monograph \textit{Fluoridation: Errors and Omissions in Experimental Trials} was published by Melbourne University Press in 1959, copies were dispatched to the press’s United States agent, Cambridge University Press. The executive director of the Nutrition
Foundation, a body funded by the American food industry, wrote to Cambridge University Press, saying “The professional standing of the Cambridge University Press among scientists and educators would seem to preclude publication of such a book by Cambridge University Press.”

Sutton also says that the type of his monograph was, without authorization, melted down soon after publication and had to be reset for the second edition only a year later. At that time, Melbourne University Press normally kept type for at least six months.

The Index to Dental Literature, published by the American Dental Association, did not include either the first or the second edition of Sutton’s book. It included negative reviews of the book, but not positive ones.

Not surprisingly, journal editors usually deny any improper behavior on their parts. In 1957, dental editors responded to charges of bias by issuing a resolution stating that “no dental journal is restrained or has been restrained from being free to publish both sides of all controversial matters.” Of course, it is quite possible for editors to believe that they are unbiased, while bias, as inferred by others, is at the same time, present.

The above cases are examples of attacks on antifluoridationists. I have heard of only one exception to this pattern. The Australian journal Simply Living has published several articles critical of fluoridation. After one of them appeared, Gordon Medcalf, a dentist, submitted a brief reply. The editor rejected it, saying that the views on fluoridation expressed in Medcalf’s article were contrary to the facts as Simply Living understood them.

The attacks against antifluoridationists predictably are documented almost entirely by antifluoridationists themselves. It is not normally considered proper to reject a scientific paper or deny a research grant simply because of a person’s views on fluoridation. Therefore, such cases are not normally publicized by profluoridationists, but are, sometimes, referred to by opponents in order to condemn the methods of the proponents.

Most of the cases have been documented by leading scientist opponents of fluoridation rather than, for example, members of citizens’ groups. There are several reasons for this.

First, leading scientist opponents attract a disproportionate share of the attacks because it is especially important to proponents to reduce the effectiveness that derives from their greater credibility. If an accountant, bricklayer, or homemaker makes claims about fluoridation, it is easy for dentists, doctors, and scientists to dismiss the claims as coming from uninformed sources. In the public debate, and in many scientific forums, the credibility of a statement relates more to the formal status of the person who makes it rather than to the content of the statement itself. For the purposes of the fluoridation debate, the claims of relevant professionals — especially those who have written and done research in the field — take on an exceptional significance.

Then, too, because most professionals have favored fluoridation, the few public opponents play a special role. If their credibility can be damaged or their activities which hurt fluoridation can be reduced, this can help change the situation from debate — however unbalanced it may be — to unanimous professional support. Therefore, the leading opponents are much more likely to be targeted for attack.

Also, leading opponents are likely to document attacks because they are prominent nodes for communication. People hear them give talks, read their articles, and, as a result, send them further information. These key figures thereby obtain masses of information, some of which they may publish as accounts of attacks on opponents.

Finally, leading opponents are more able to publish accounts of attacks — especially attacks on themselves — because they have little to lose and something to gain by doing this. They are already prominent in their opposition. Others may not want to spend their lives as antifluoridation partisans, but may simply want to continue work as dentists or medical researchers. For such people, to publicize attacks on themselves would be to bring further attention to their activities and
perhaps induce further problems. A safer path is often to simply say nothing and avoid arousing the antipathy of fluoridation proponents.

Attacks on opponents probably have the greatest impact on those who are less prominent in the debate. They provide moral lessons in what may happen to those who take up the “wrong stand.”

The normal idea of professional practice holds that measures such as dismissal are taken only against those who are incompetent, unethical, or simply “not good enough.” A decision to reject an article submitted to a professional journal is supposed to take place on the basis of peer review, itself based on scientific or scholarly criteria. Membership in professional societies is normally withdrawn only from those who have severely breached professional ethics. How, then, are the sorts of attacks on antifluoridationists described here to be interpreted?

Some profluoridationists perhaps see continued open opposition to fluoridation as evidence of poor judgment, scientific incompetence, unethical behavior, or worse. The imposition of measures against certain opponents is quite justifiable in this context. Furthermore, no doubt, some of the cases can be explained (or explained away) as exaggerated accounts or paranoid interpretations by people with an ax to grind. But this does not explain the full pattern of attacks.

Most antifluoridationists see the use of professional power against opponents as a violation of professional principles, and as evidence of the unscrupulous behavior of promoters of fluoridation. Opponents of fluoridation frequently raise these cases of suppression as showing the political rather than the scientific basis for the promotion of fluoridation. By highlighting discrepancies between the stated norms of scientific behavior and the actual behavior of certain scientists, the opponents use the category of unjustifiable behavior as a resource in their struggle.

A middle-of-the-road approach might categorize these examples as unfortunate excesses, not representing proper behavior and possibly being counterproductive for the proponents. But, since the opponents are believed to be wrong and have so little professional credibility, it is not worth making a big fuss about particular cases.

This apparently moderate and balanced view ignores one thing: the organized efforts within the dental profession to denigrate the reputations of antifluoridationists. The dossiers published and distributed by the American Dental Association create a climate of contempt, in which attacks on antifluoridationists become more acceptable. The opponents are, the dossiers suggest, only cranks anyway.

In summary, the profluoridationists, through their influence in dental and medical associations, their positions and influence with health authorities — especially the U.S. Public Health Service — and their influence over the editorial policies of journals and publishers, have created a climate in which some zealous proponents use a variety of aggressive techniques to stop the expression of antifluoridation views by professionals.

This point again illustrates the impossibility of assessing the fluoridation issue without a full consideration of the dimension of power. An assessment of the scientific evidence is incomplete without knowledge of what research may have been inhibited from being done in the first place, prevented from being published, or relegated to marginal status by attacks on the credibility of the researchers. To assess the impact of these processes, it is necessary to understand the exercise of power both in the fluoridation controversy itself and in the society in which it takes place. To proceed in the analysis, I now turn to the issue of professional power.

**Professional Power**

It might seem that activities such as character assassination, maintenance and distribution of dossiers, blocking of grants, removal from professional societies, and denial of publication are incompatible with proper behavior for professionals. The usual idea of a profession is of a group of skilled practitioners who act collectively to ensure high standards, ethical
behavior, and service to the public. Indeed, a common explanation for the dental profession’s support for fluoridation is the altruistic commitment of the occupation to community dental health, even at the expense of reduced earnings. Surely, the unsavory practices involved in “suppression of dissent” on an issue such as fluoridation would not be considered as proper professional conduct.

The explanation for this apparent contradiction lies in a reexamination of the nature of professions. The traditional view of professions as bodies designed to serve community welfare has been challenged since the 1970s by a different analysis. In this alternative view, a profession is essentially a way of organizing an occupation in order to gain and protect wealth and status. Using this perspective, it can be argued that the interests of the profession are not necessarily hurt by the promotion of fluoridation.

The first point here is that the supporters of fluoridation are not all the same. To say that dentists stand only to lose business because of fluoridation, and that, therefore, they are entirely altruistic in supporting it, is to hide differing interests within the dental profession. Dental researchers who have built a reputation on research into and support for fluoridation constitute one small group with a clear career and personal interest in promoting fluoridation. For example, Noel Martin did some of the early research in Australia into the effect of fluorides on tooth decay. His research in this area provided one basis for his academic advancement at the University of Sydney, where he became a professor and Dean of the Dental School. If history had been different and fluoridation in Australia had never gained acceptance, someone like Noel Martin might never have gained his status and influence.

There is no doubt that Noel Martin, like most other researchers and promoters of fluoridation, is completely sincere in his support for the measure. An analysis of the promotion of fluoridation in terms of interests does not depend on any assessment of the motivations of individuals. What it does depend on is the existence of some benefit, material or symbolic, accruing to individuals or groups. A person such as Noel Martin may gain some career benefit from promotion of fluoridation while being, personally, completely disinterested in considerations of prestige or career.

The same process can be explained in terms of the structure of the dental profession. The hierarchies of government health departments, university dental schools, and professional dental associations provide opportunities for individuals to gain in terms of income, status, and power. Promotion of fluoridation is one path to this income, status, and power — assuming that fluoridation is or becomes widely accepted as a “good thing” and, therefore, that those who lead the profession toward it can claim to be worthy of plum positions.

There is also a psychological factor involved here — namely, the commitment that develops when one campaigns for a cause. Most people who take a conspicuous public stand on a subject become more reluctant to admit they were wrong. They are more likely to search out supporting evidence and sympathetic people. As described in chapter 3, the polarization of viewpoints on fluoridation owes much to the ongoing public debate, in which a backdown by any prominent individual would be highly distressing to those with the same view.

Psychological commitment explains some of the passion and rigidity of viewpoint in the fluoridation debate, but it does not explain why so many dentists support fluoridation. One important factor here is dental education. Dental students are more often taught the “correct view” rather than taught to make a critical and independent assessment of the evidence and arguments. When profluoridationists are influential in the teaching of preventive dentistry, most students are taught the fluoridation paradigm. For example, the Sydney University Dental School has turned out a whole generation of profluoridation dentists, thanks to the efforts of leading proponents Noel Martin and Graham Craig. When teachers are not solidly profluoridation, students are also less so.
Another factor is the image of the profession as a whole. A comparison to the medical profession provides a useful starting point. It can be said that the history of medicine is something that the medical profession needs to forget. The era of “scientific medicine” really began only during this century. It is not so long ago that many methods used by physicians did more harm than good — such as applying leeches or delivering babies in contaminated conditions. The status and power of the medical occupation was immensely improved by the discoveries of antibiotics and other “wonder drugs.”

A number of critics of medicine argue that most of the reduction in mortality from common diseases such as tuberculosis and typhoid occurred before the medical “breakthroughs” normally claimed to have been responsible. This decline in incidence and mortality happened because of social improvements, such as public hygiene, better working conditions, and better nutrition. According to this critique, medical science, although responsible for some valuable developments, has unjustifiably been credited for health improvements for which it was not primarily responsible.

For the purposes of the argument here, however, it doesn’t matter so much whether medical breakthroughs are really responsible for dramatic reductions in mortality from particular diseases. The point is that most people think they are, and the profession has fostered this belief and used it to its advantage. Massive government funding of clinical treatment and medical research is provided, even in countries where medicine is ostensibly private. This sort of funding would be harder to justify without the reputation of medicine as a worker of miracles.

While more than public image is involved in explaining the power of the medical profession, that image is important. And it is at the level of image that the dental profession usually comes off second best.

Dentistry has taken advantage of scientific and technological developments. Dentists routinely use X-rays, anesthetics, molding techniques, new bonding materials, and the like. These techniques, associated with modern science and technology, help raise the status of dentistry. But none of these techniques is uniquely associated with dentistry as a great advance. Furthermore, none of these techniques can claim to have caused a miraculous reduction in dental problems, similar to the claims for some of the “wonder” drugs used in medicine.

Fluoride is the best candidate for dentistry’s claim to a scientific breakthrough. The early and later research was done by dental researchers. The measure claims a massive and dramatic improvement in dental health and the method is via a “magic bullet,” an added substance that causes the improvement. In all these ways, fluoride against tooth decay mimics the established pattern of medical breakthroughs. In the words of a major Canadian report on preventive dental services, “The 30 to 40 years of epidemiological studies which established the relationship of natural fluoride in the drinking water to the prevention of tooth decay is dentistry’s most distinguished contribution to improving the public’s oral health.” A document published by the Australian Department of Health states more baldly that “Fluoridation of water is perhaps the greatest single development in the history of dentistry.”

Fluoride thus provides the basis for an elevation of the public image of the entire dental profession. Fluoridation becomes one way for dentistry to distinguish itself from “technical” occupations, such as physiotherapy or auto repair. The implementation of fluoridation requires sophisticated scientific understanding — such as epidemiology required to measure its effectiveness — and this provides a knowledge base from which dentistry can claim a higher status. So, it can be argued that fluoridation provides the basis for an elevation of the status of the dental profession as a whole.

As in the case of medical breakthroughs, it doesn’t matter whether fluoridation is really responsible for a massive reduction in tooth decay. What counts is that most dentists think it is, and that they have been able to convince
enough people in the community of the accomplishment.

John Colquhoun has carried out a study arguing that, in New Zealand, the rate of tooth decay was constantly declining for decades before fluoridation and fluoride toothpastes were introduced, and that their introduction had no dramatic effect on the rate of decline. Colquhoun’s results are very similar to those observed for diseases such as tuberculosis.

Earlier in the century, British dentists were receptive to the unfounded theory of oral sepsis, which posited that infections in the mouth led to disease in other parts of the body. To stop this alleged problem, teeth were extracted. According to Gilles Dussault and Aubrey Sheiham, the theory’s lack of scientific foundation was of little relevance, so long as it seemed sound to dentists and doctors. They argue that the acceptance of the theory of oral sepsis was “determined as much by its capacity to fit the social and economic needs of practitioners as by its apparent validity or its therapeutic virtues.”

But what about the objection that dentists will be worse off if tooth decay is reduced by a large fraction? Once again a comparison with medicine is valuable.

Doctors were not put out of business after the introduction of vaccines and antibiotics because of two main reasons: there are plenty of other medical problems for doctors to treat, and entry to medicine is influenced by the medical profession itself. Both these factors apply to dentistry as well.

The traditional idea of a profession — of which the prototypes are the clergy, law, and medicine — is of a “calling” in which work is done to serve community welfare according to special ethical standards and with control over entry and performance by colleagues. The revisionist view is that a profession is really just another occupation, except that, by claiming to have special standards and requirements, the members of the occupation attempt to gain money, power, and prestige. Trade unions and industrial struggle for better wages and conditions constitute one strategy for members of an occupation. Claiming professional status is a somewhat different strategy.

A key characteristic of professions is that they regulate entrance to an occupation. For the most lucrative professions — medicine and law — entry to the occupation is regulated by the state. This is done through government-supported and restricted training in higher educational institutions and through licensing by government-authorized bodies. Not just anyone can set up practice as a dentist. Unlicensed “quacks” will be prosecuted.

In some other areas — such as becoming a potter, a singer, or an athlete — no formal qualifications are required. Success is dependent mainly on public perceptions of performance. By contrast, in licensed occupations, the supply of qualified practitioners is usually limited so that wages are kept up. Once granted a license to practice in the occupation, there is little or no market test of the quality of one’s performance. Only a tiny minority of doctors or dentists is struck from the register for poor-quality work. In short, a profession is a protected monopoly.

Why should the state grant such a license to an occupation? The process involved is complex, but it can be boiled down to a power struggle. A profession is basically an occupation in which some members have successfully mobilized around a claim to a monopoly over certain knowledge and skills, and won over key parts of the state to provide it with legitimacy through licensing. The more effective the mobilization of practitioners, the more effective the exclusion of competing practitioners and the more likely the winning of concessions from the state.

In countries where doctors and lawyers have been most successful, they are strongly protected by state licensing but weakly regulated by the state itself. This is the case in the United States, where doctors and lawyers are powerful and their average incomes are high.

In Britain, by contrast, the medical profession is similarly protected, but there is strong intervention in provision of professional services through the national health service. In the Soviet Union, the state is even more
interventionist, controlling most of the conditions of work. Relative salaries of doctors are much lower, and there is no immediate analog for the legal profession as known in the West.

Those in other occupations are well aware of the advantages of holding a monopoly over the exercise of skills as licensed by the state, and many of them have sought state regulation as a way to improve their conditions. In various parts of the United States, for example, it is illegal to do plumbing, electrical wiring, or tile laying without a license. In this way, full-time plumbers, electricians, and tile-layers seek to improve their status and income.\(^{55}\)

This perspective on professions does not exclude service to the public, but neither does it guarantee it. The key to a profession’s success lies in convincing its clients that its services are both necessary and unobtainable elsewhere. Even if the profession does little or nothing helpful — such as the medical profession until perhaps half a century ago, before which there were few cures for diagnosed diseases — both the professionals and the clients may sincerely believe that the services are essential, beneficial, and provided out of altruistic motives. The practitioners may believe they are altruistic, while, at the same time, the practice of the profession provides them with both material and symbolic benefits.

**DENTISTRY AND TOOTH DECAY**

This perspective on professions has been systematically applied to dentistry by Peter Davis in his book *The Social Context of Dentistry*.\(^{56}\) Davis describes the rapid professionalization of dentistry and the way in which dental practice has developed to combine clinical science and personal delivery of services.

The main emphasis in dentistry has been on treatment of individuals rather than changing institutions; this provides traditional dental practitioners with a continuing professional role. Most dental interventions are either at the treatment stage, such as restorative measures, or aimed at the individual, such as attempts to change individual dietary practices rather than policies of the food industry.

In this context, the promotion of fluoridation is an apparent anomaly. Unlike most of dentistry, fluoridation is a preventive measure directed at the collective level, namely community water supplies.

Davis does not systematically discuss the fluoridation issue. However, some preliminary observations can be made on how the perspective on professions as occupational power systems can also explain why reductions in tooth decay are not threatening to dentists.

Even in earlier decades when tooth decay was much more widespread in the community, fillings and extractions accounted for only part of any dental practice. As tooth decay has declined in most industrialized countries, this has not meant unemployment or drastically lowered incomes for dentists.

First, in most countries there are simply not enough dentists to treat all the dental problems in the community.\(^{57}\) There is a large untapped demand, and at least some of the many people needing treatment are able to pay for it in countries where there is no public dental scheme. There have been plenty of additional patients to counteract loss of income due to declining tooth decay rates. Some effort, however, may be required to get more people to go to dentists. School dental programs and public education campaigns serve this function.

Second, restorative dentistry has gradually replaced extractive dentistry. In earlier years, a bad set of teeth would simply be removed. Today, the preference is to retain as many teeth as possible and to use crowns, bridges, and other devices to keep them. In addition, regular check-ups and cleaning have become standard. All this requires a lot more treatment and costs more. Increased standards of living mean that more people can afford to have this done and, thereby, keep dentists in business.

For example, orthodontics, the branch of dentistry concerned with the straightening of irregular teeth, has expanded enormously in the past several decades. Early in the century, crooked and misplaced teeth were simply lived with. Today, it is commonplace for children to
have braces and other treatments to bring teeth into a more pleasing alignment. Orthodontic treatment for adults is also becoming popular.

There has been plenty of time for changes to occur in dental practice to match altered conditions. This is because changes in dental health have not occurred overnight. Even when dramatic reductions in tooth decay have been claimed — as due to fluoridation — this applies only to particular cohorts of children. The overall rate of dental problems, including nondecay problems, has changed more gradually.

A third reason why reduced tooth decay rates have not put dentists out of business is that the supply of dentists is regulated in part by the profession itself. It is impossible for people “off the street” to set themselves up as dentists. They must be licensed by a professional body. Usually, this means years of training in a certified dental school. Entry into dental schools, then, is a crucial point for controlling the supply of dentists. It is in the interests of practicing dentists as a whole not to allow excessive numbers of entrants into the field — assuming that current numbers can adequately cope with those who are able to pay for dental treatment — since this would reduce average incomes.

In Australia, for example, dentistry is taught at universities. There is a limited number of positions for students, and, because dentistry is a lucrative career, entry into the dental course is highly competitive. A very high score on the relevant entrance examination is required. It is also very difficult to get into medicine and law, two other professional areas with attractive career prospects. By comparison, university-entry requirements for science and humanities are relatively low, since career prospects in these areas are not nearly so lucrative.

Entry requirements into dentistry are not high because special aptitudes are required of dentists. Indeed, the entrance examination has no special relevance to dentistry. They are high because many more students want to become dentists than are allowed to do so. The reason dentistry is so popular is precisely because the number of dentists is limited, and, therefore, their average incomes are higher than in most other occupations.

There are, then, at least three reasons why reductions in tooth decay are not particularly threatening to the financial interests of dentists. First, there were never enough dentists to start with. Second, dental practices are changing towards more labor-intensive cleaning and restoration. And third, the dental profession regulates entry, preventing a severe over-supply of dentists.

Undoubtedly, many dentists are personally altruistic in supporting fluoridation in the hopes of massive reductions in tooth decay, even though they realize that their practices may suffer to some degree. But this altruism must be understood within the occupational situation of dentists, a situation buffering them from any dramatic loss of income.

This, then, is an alternative perspective on why so many dentists have supported, or not resisted, fluoridation. There are a small number of promoters — especially those in research positions — who have built careers on fluoridation and who have reputations as well as many years of personal commitment at stake.

Most dentists are not active promoters, but they do support or accept fluoridation. As a “miracle” treatment provided by the profession, fluoridation promises to raise the status of the occupation of dentistry in a way similar to medical “miracles.” In any case, most dentists do, indeed, care about the suffering of their patients, and fluoridation promises to reduce this without suddenly eliminating the need for regular dental treatment. In this perspective, altruism is quite compatible with maintenance of professional status and income.

There is some evidence that can be interpreted as supporting this perspective. A study in 1967 found that, when later-year dental students were asked the question, “if a cure of dental caries is found in the next 5 years, do you feel that this benefit to mankind will affect your income as a dentist?,” twice as many answered “No” as answered “Yes.”

A detailed comparison by supporters of fluoridation of dental practices in matched
pairs of fluoridated and unfluoridated American communities concluded that “fluoridation did not affect dentists’ incomes, fees, and nature of treatment to any significant degree.”

This study found that there were slightly fewer dentists in fluoridated communities and that they had higher salaries.

Antifluoridationists also point to statistics showing that the number of dentists in particular communities has not decreased after fluoridation, but has often increased. But a detailed test of the competing perspectives on why dentists support fluoridation has not been made.

It is possible to spell out a number of hypotheses on the basis of the just-mentioned perspective. For example, it predicts that support for fluoridation would be stronger, other things being equal, in countries where the profession itself has greater control over entry into the profession. It predicts that support for fluoridation would be greater where there is an undersupply of dentists. It predicts that support for fluoridation would be greater among dental researchers and prominent figures in the profession. These and other predictions remain to be tested. The amount of cross-national data on the fluoridation controversy is so limited as to allow widely divergent interpretations of available evidence.

One other point is worth noting. Once the dental profession made a strong commitment to fluoridation, it staked its reputation on the measure. It became very difficult to reverse or even modify the policy, because this would be tantamount to admitting that the dental experts were wrong — both scientifically and ethically — in promoting an insufficiently tested procedure.

This commitment applies even when there are good reasons to change policy. One supporter of fluoridation, Dennis H. Leverett, noted in a 1982 article in the prestigious journal Science that the prevalence of fluoridation has meant that fluoride is increasingly found throughout a variety of foods, such as reconstituted fruit juices. Therefore, people are getting much more fluoride in their diet than they would have in earlier years.

Leverett commented, “the definition of the optimum concentration of fluoride in community water supplies needs to be reassessed. It is important to remember that efficacy of fluoridation and standards for its implementation were established when water fluoridation was the exception, rather than the rule.”

This point has not been taken up openly by proponents of fluoridation. In the context of the ongoing debate, it would be taken by opponents as a sign of weakness and retreat. Instead, Leverett was privately criticized, especially by proponents within the USPHS, for expressing this view.

In 1987, A. S. Gray, director of the Division of Dental Health Services in the British Columbia Ministry of Health, made comments about reconsidering advice about fluoridation in an article in the Journal of the Canadian Dental Association. Noting that decay rates in British Columbia, which is mostly unfluoridated, are less than in other Canadian provinces with more fluoridation — and are continuing to decline — he states that “we may not need fluoridation as much as we once did.” But, rather than becoming a talking point for the proponents, Gray’s article was quickly picked up by antifluoridationists who have widely circulated quotes from it. This shows the difficulty in trying to modify a policy that has been long defended in a highly polarized situation.

**Conclusion**

This analysis of the dental profession as a system for organizing the power of an occupation is valuable for understanding the attack on opponents of fluoridation. Fluoridation was vital to the careers of some researchers and to the image of the profession as a whole. In the struggle over the issue, any means available were liable to be used. It just so happened that the proponents of fluoridation were able to capture control of professional resources in the United States and many other countries. These resources —
including access to professional journals, membership of dental associations, and availability of research funds — were then used in the struggle against opponents.

The actual details of attacks on opponents cannot be predicted in this manner, since decisions to threaten a critic depend on individuals and particular circumstances. What can be said is that the pattern of attacks reflects the distribution of power in the controversy. Because the proponents have access to resources associated with the dental profession, they are the ones capable of making these sorts of attacks — and they sometimes do!

The limits to attacks on opponents are the limits of professional power. There has been little violence in the fluoridation debate, because neither side has any special hold over the legitimate use of violence. However, if fluoridation had been promoted or opposed by, for example, the military, then it is likely that violence, or the threat of violence, would have been used to promote or oppose it.

There are also tactical considerations that limit the use of professional power. The abuse of power can be counterproductive. Striking dentists off professional rolls is a very serious step, and many profluoridation dentists are likely to be reluctant to see this happen simply on the basis of a dentist’s public expression of views against fluoridation. There is always the danger of generating a countermovement of dentists opposed to such serious measures.

Antifluoridationists may seem to be more pure-minded, since they have not been responsible for a similar number and range of attacks on proponents. But, arguably, this is simply because they have not had access to the same professional resources as the proponents. In many of their writings, antifluoridationists project themselves as highly intolerant of proponents. It is safe to predict that should antifluoridationists capture control of the dental profession in particular countries, the stage would be set for similar sorts of attacks, this time on dissident proponents.

This analysis of the role of professional power can readily be extended to the use of other sorts of power in the struggle. Both proponents and opponents have attempted to influence politicians, trade unions, the mass media, and community groups. Each side uses whatever resources it can acquire in its struggle, whether from support by a political party, popular expression of support through rallies, letters to newspapers, or the commitment of supporters who are willing to distribute leaflets and arrange speaking engagements for civic organizations. The antifluoridationists have been more conspicuous in doing this, especially in relation to referendums, partly because they have not had the authoritative support of dental bodies. But especially in countries with decentralized decision making, such as the United States, both sides have done enormous amounts of day-to-day work which is typical of communities organizing on all sorts of issues.

Because the resources associated with the dental profession are so powerful, it has been vital for the success of fluoridation to capture control of the profession in the sense of having support from the leading figures. From this perspective, the early efforts by the “Wisconsin dentists” and other proponents to obtain endorsement by the USPHS, the ADA, and the AMA were crucial. Without professional support for fluoridation, it would have been very difficult to implement the measure.

Following the vital early step of capturing professional support for fluoridation, it has continued to be vital to maintain the appearance of professional unanimity. As long as the opponents have no scientific or professional credibility, they can be more easily typecast as unknowledgeable cranks, and thus rejected.

This strategy has depended on discouraging professionals from taking vocal open stands against fluoridation. In this context, the attacks on opponents are a logical outgrowth of the initial way fluoridation was promoted. In the highly polarized and vehement controversy, it was only to be expected that professional power would be used for professional attack.
NOTES


1. An attempt to have a person barred from practicing dentistry normally involves rhetoric, too, as the following examples illustrate. The point I am trying to make here could be described as a distinction between rhetoric used to threaten a person’s credibility (chapter 4) and rhetoric used to threaten a person’s physical practices, including publications, research work, and job (this chapter). Even this distinction contains some conceptual messiness. My aim is less to establish a conceptual classification of the exercise of power than to demonstrate the power dynamics of the fluoridation controversy.


7. Yiamouyiannis, op. cit.: 158-159.


10. Ibid., 201


13. Waldbott, op. cit., 140-141. See also Harry M. Raulet, “The Health Professional and the Fluoridation Issue: A Case of Role Conflict,” Journal of Social Issues, vol. 17, no. 4 (1961): 45-54, at 46. “In neither city did a local physician or dentist work actively and openly against the fluoridation proposal, but the proponents, very much concerned with professional solidarity in the matter, were quite bitter toward their few colleagues who refused to sign the endorsement.”

15. Carol Farkas, letter to Brian Martin, dated 6 April 1986.


17. Waldbott, op cit., 249.


19. Ibid., 107.


23. Mark Donohoe, letter, Central Coast Express (18 June 1986): 6; M. Walsh, Acting Secretary, Medical Board of New South Wales, letter to M. Donohoe (9 September 1986).


25. Ibid., 232.

26. Ibid.

27. Ibid., 311-312. This incident is also reported by John Colquhoun and Robert Mann in “The Hastings Fluoridation Experiment: Science or Swindle?” The Ecologist, vol. 16, no. 6 (1986): 243-248, at 247.

28. This highly important point is amply documented in Edward Groth III in his review of the scientific literature, Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area and Fluoridation of Community Water Supplies, Ph.D. dissertation, Stanford University (1973), chapter 5. Groth states on page 276 that “A consistent, serious, flaw in this body of research, and one which is probably closely related to the quality of the studies, is commitment to predetermined conclusions on the part of the investigators.”


32. Waldbott, op. cit., 323.

33. Waldbott et al., op. cit., 334-335; Walker, op. cit., 145-146.


41. A possible exception is the more neutral analysis of Groth, op. cit., who lists a number of cases on pages 179-185. However, many proponents would consider Groth to be a de facto opponent, partly because he documents attacks on opponents.

42. I thank Edward Groth III for emphasizing this point to me.

43. The fluoridation debate is not the only scientific debate where these sorts of attacks have been documented. There are numerous examples from around the world in which scientists critical of nuclear power have been transferred, censored, lost research funds, and been sacked from jobs. See Leslie J. Freeman, *Nuclear Witnesses*, New York: Norton (1981); and Brian Martin, “Nuclear Suppression,” *Science and Public Policy*, vol. 13, no. 6 (December 1986): 312-320. The characteristic of cases of “suppression of dissent” is that the target has done research or spoken out critically of nuclear power, while others with equivalent work records have not been attacked in the same way.

Nuclear scientists and engineers working in government research organizations or corporations can be attacked directly by management who support nuclear power. Critics in universities are harder to attack, since university administrations usually have no direct commitment to nuclear power. University scientists are vulnerable to having research grants cut off, and, in some cases, to the blocking of tenure or promotion. This may occur as a result of outside pressure, usually operating through connections between powerful figures inside the university and pronuclear groups outside. Nevertheless, scientist opponents in universities are much more protected from attack than those in government or industry.

Another area where these sorts of attacks on scientist critics have been well documented is pesticides. Rachel Carson, author of the immensely influential *Silent Spring*, was subject to vicious attacks, although her independent position provided protection. See Frank Graham, Jr., *Since Silent Spring*, Boston: Houghton Mifflin (1970). University critics have suffered the same gamut of attacks as have critics of nuclear power, while few inside government — not to mention the chemical industry — have had the inclination or temerity to speak up critically. See Samuel S. Epstein, *The Politics of Cancer*, San Francisco: Sierra Club Books (1978); and Robert van den Bosch, *The Pesticide Conspiracy*, Garden City, N.Y.: Doubleday (1978).


45. I thank Edward Groth III for emphasizing this point to me.

46. Students in one of my classes interviewed local dentists on their views about fluoridation. While neither a complete nor a random sample was involved, the results were striking. Eighteen of twenty dentists interviewed were graduates of Sydney University, and every one of the eighteen supported fluoridation. Without exception, they thought the dental school had presented them with strongly profluoridation views, and some mentioned that contrary views were excluded or denigrated.


49. Davis, op. cit., 120.


56. Davis, op. cit.

57. Ibid., 126-129.

58. My argument here is greatly indebted to Varney, op. cit.


62. I thank Albert Burgstahler and Edward Groth III for emphasizing this point about ethics.

Note that Leverett’s article appeared in *Science*, not a dental journal.

64. Edward Groth III, in a letter to Brian Martin, dated 8 December 1988, said that “Leverett was not being innovative … he was just saying openly what all of his fellow pros were saying whenever the issue of total fluoride intake came up.” But there has been no move to do the research to see whether total fluoride dosage is so high that water fluoride levels should be lowered.

65. Leverett’s career apparently has not suffered as a result of his *Science* paper.


67. Albert Burgstahler provided me with copies of a letter from Dennis H. Leverett to David Werdegar, Health Director, San Francisco Health Department, dated 17 July 1985; and a letter from A. S. Gray to John Osterman, Lakeshore General Hospital, Quebec, dated 7 March 1988, in which they both appear to renounce any deviation from the standard profluoridation line. This again suggests the powerful pressures to maintain set positions.

68. Edward Groth III points out in a letter to Brian Martin, dated 8 December 1988, that the sides are not perfectly symmetrical, since the antifluoridationists have only one means to prevent the health risks and coercion they see to be associated with fluoridation, whereas the proponents have other options to promote dental public health. Evidence for and against the view that opponents, given the chance, would suppress proponents remains to be collected. Evidence in some other areas — such as the plight of left-wing and right-wing critics under regimes of the opposite orientation — supports the symmetry thesis.
A corporate connection?

Proponents typically portray support for fluoridation as coming from responsible professionals, community organizations, and citizens. For example, one writer says that “Proponents of fluoridation have included dentists and their professional organizations, public health officials, and a wide variety of civic groups, from parent-teacher associations to veterans groups.”

The proponents often describe the opposition, by contrast, as associated with groups with special belief systems. The same writer states that “The opposition has consisted of a coalition of groups with varied interests, including the politically ultraconservative John Birch Society, health-food enthusiasts, chiropractors, and some members of religious groups such as Christian Scientists.” In other words, proponents are responsible members of the community, whereas opponents are likely to be from groups with axes to grind.

Opponents offer a different picture. They portray opposition as coming from a wide cross section of the community, including a substantial fraction of dental and medical professionals who are deterred from taking an open stand. Some opponents see support for fluoridation as driven by vested interests, including aluminum and fertilizer companies wanting to get rid of fluoride wastes, and government bureaucracies and dental elites seeking to impose their wills on the population. In short, opponents are ordinary concerned members of the community, whereas support for fluoridation derives from financial and bureaucratic vested interests.

In this chapter, I pursue the role of interest groups in supporting and opposing fluoridation, a task begun in the previous chapter with the analysis of the role of the dental profession.

THE OPPOSITION

The standard ways in which opposition to fluoridation has been explained are in terms of irrationality, alienation, or confusion. All of these have been explanations in terms of problems suffered by individuals. Instead, I seek explanations in terms of “interests” which typically involve money, power, or prestige. Are there any groups with an interest in opposing fluoridation?

The only group with an obvious interest in this regard is dentists. Dentists might be thought to have a professional (financial) interest in opposing fluoridation, since they believe it will drastically reduce tooth decay and therefore reduce the demand for their services. But dentists, by and large, do not oppose fluoridation. It is hard to find any similarly obvious reasons, in terms of material interests, that exist for the opposition.

There is very little money to be gained by opposing fluoridation. Some antifluoridation groups benefit financially from sales of water purifiers, but this is far from providing a material interest in stopping fluoridation. After all, their sales would decline if fluoridation were ended. At most, they would have an interest in a continuing controversy in fluoridated areas.

Many members of the health-food movement, especially stores selling so-called health foods, have been involved in the opposition. Part of the promotion of health foods consists in establishing their purity and naturalness in terms of being unrefined, free from added colorings and flavorings, and grown in the absence of pesticides and artificial fertilizers. Those who want to eat so-called natural foods are also likely to want to drink what they consider to be pure water; adding fluoride can be claimed as making water impure.

There is not much of a link here involving money or political power. Indeed, health-food
shops stand to make money by selling unfluoridated water in fluoridated areas. The health-food industry is much more threatened by measures such as laws to limit sales of vitamins, against which they have strongly mobilized. Opposition to fluoridation has not been backed by the organized power of the health-food industry in the same way that fluoridation has been promoted by dental associations. Many people who consider themselves to be supporters of health foods oppose fluoridation, but only a minority of these people take an active role in the debate.

The connection is more at the level of beliefs than of material interests. If "interests" can be said to be involved, it would be an interest in publicly maintaining a coherent stand against various threats to so-called natural food and drink.

Similar sorts of comments apply to the participation of chiropractors and Christian Scientists in the opposition. In both cases, fluoridation is opposed as a threat to the sort of society these groups prefer. While some individual opponents have come from the ranks of chiropractors and Christian Scientists, neither professional associations nor churches have taken a leading role.

Especially in the 1950s and in the United States, extremist right-wing and racist groups were opposed to fluoridation, including the John Birch Society and the Ku Klux Klan in the United States and the League of Rights in Australia. Opposition to fluoridation provided a vehicle for such groups to vent their opposition to "big government." But the antifluoridation rhetoric of such groups apparently has not persisted much past the cold-war period of the 1950s, and so does not provide a satisfactory explanation for opposition to fluoridation. The significance of the extreme right's involvement against fluoridation — even in the early years — remains to be properly investigated.

On the other hand, a wide-circulation weekly right-wing newspaper, The Spotlight, has published antifluoridation articles in recent years, as well as many other articles advocating pure foods and numerous advertisements for vitamins and health foods. But Liberty Lobby, publisher of The Spotlight, is inconspicuous in antifluoridation campaigning. Certainly profluoridation groups have not articulated such a connection. This limited evidence suggests that certain right-wing groups may adopt antifluoridationism if it has widespread social support, but they are not the driving forces behind it.

Another set of people involved in the opposition, more amenable to being "explained," is those who are employed by national organizations. Their opposition can be attributed to their personal gain from wages. This approach does not carry one very far.

The closest thing to a national organization in the United States in the 1950s and 1960s was the publication National Fluoridation News. This was originally edited and published by Edith Waldbott, George Waldbott's wife. But it was hardly a vehicle for personal gain. Waldbott himself said he made a point of never accepting payment from patients for complaints thought to be related to fluoride in order to avoid any taint of self-interest.

More recently, the National Health Federation has been involved in campaigning against fluoridation, especially when it employed John Yiamouyiannis. It is possible to explain the opposition of Yiamouyiannis by the fact that he was paid to do work compatible with the antifluoridation stand of the NHF. But another explanation is that Yiamouyiannis was willing to work for such a group because he was already convinced of the case against fluoridation. After all, Yiamouyiannis had opposed fluoridation before joining the NHF, and, since leaving it, he has continued antifluoridation campaigning with the Center for Health Action, in spite of no longer receiving a salary for his work. Furthermore, there is no obvious financial or political interest behind the involvement of the NHF in opposition to fluoridation.

In summary, the opposition to fluoridation is not easily explained in terms of money, power, or prestige to be gained by identifiable groups. This is compatible with the simple observation that the antifluoridation movement is an opposition movement. It has no obvious
positive program of its own, but, instead, is basically a reaction against initiatives by the proponents. This suggests that it might be more fruitful to look further at the role of interests in the promotion of fluoridation.

**The Proponents**

In attacking fluoridation, opponents have made various claims about who is really behind it. Some right-wing groups have said that fluoridation is a Communist plot to sap the health of Americans. A more common theme is that fluoridation is being forced on people by government, meaning a type of bureaucratic “big brother.” But these claims have been mainly rhetorical, and not backed up with much argument or evidence.

Just because these claims are unrigorous does not mean that they are necessarily wrong. But it makes sense to pursue the more carefully crafted arguments first. The two most developed arguments focus on the role of the dental profession and of particular types of corporations in promoting fluoridation. The role of the dental profession, discussed in the previous chapter, is quite conspicuous. The role of corporations is less obvious, but some opponents have pursued this argument.

There are three types of corporations with a potential financial interest in fluoridation: first, aluminum and fertilizer companies, and other producers of fluoride waste; second, producers of sugary foods; and third, producers of fluoride toothpastes, mouthwashes, and similar products.

**Aluminum and Fertilizer Companies**

One of the major wastes produced during the production of aluminum is fluoride. It is produced by aluminum companies in massive amounts, enough to seriously pollute whole areas of the countryside. Fluoride can appear in the form of a sludge that must be disposed of somewhere — typically in landfills — or may be airborne. Recycling the waste is possible, but can be very expensive.

In the United States, at least since the 1940s, farmers, local communities, and others have protested against companies whose fluoride emissions have caused economic loss and environmental harm. Damages were awarded in a number of court cases against the polluting companies. Thus, fluoride wastes were, and continue to be, not only a serious public relations problem but also a potentially serious financial problem. The companies must either install expensive antipollution equipment or risk costly legal suits.

In the simplest explanation, aluminum companies supported and promoted fluoridation because they were able to profit by selling what would otherwise be waste material to be put into public water supplies. A few bits of evidence are frequently cited in support of this claim.

The trend in the 1930s was to remove fluoride from water. Waterworks engineers recommended that the maximum level of fluoride in water be set at 0.1 parts per million. This would allow a factor of 10 as the margin of safety. A level of 1.0 ppm was considered to be the maximum allowable by the United States Public Health Service (USPHS).

Contradicting this trend for lower fluoride levels was the recommendation to add fluoride, first made in 1939 by Gerald J. Cox who was then working at the Mellon Institute, which had been founded by Andrew and Richard Mellon, former owners of the Aluminum Company of America. The Mellon Institute provided facilities for research in a range of areas, and useful findings were turned over to the relevant manufacturer.

Cox later went on to become a major promoter of fluoridation. He was, for example, on the Food and Nutrition Board of the National Research Council, where he presented arguments for fluoridation. This body provided close links between government and industry.

Another early link between aluminum companies and fluoride research was the Kettering Laboratory. George Waldcott, Albert Burgstahler, and Lewis McKinney wrote that “Kettering Institute scientist E. J. Largent, who subsequently became consultant for Reynolds Metals Company, has written a book entitled *Fluorosis: The Health Aspects of*
Fluorine Compounds, which was expressly designed, as indicated on its jacket, to ‘aid industry in law suits arising from fluoride damage.’ This book has been used as a reference source by many physicians and health organizations and strongly supports the use of fluoride in drinking water and discounts or minimizes its toxicological effects.” Antifluoridationists often reproduce an advertisement from a 1950 issue of the Journal of the American Water Works Association, which says “Fluoridate your water with confidence. Use high purity Alcoa sodium fluoride.” This advertisement symbolizes the connection between aluminum companies and fluoridation.

The argument that aluminum companies are implicated in the promotion of fluoridation rests on two claims. First, fluoridation serves the interests of the companies. Second, there were some links between the companies and the early promotion of fluoridation.

Does fluoridation serve the interests of aluminum companies? The usual connection spelled out is that the companies have a direct financial interest in selling fluoride, as in Alcoa’s advertisement for sodium fluoride. In contrast is the argument that fluoride wastes from aluminum smelters cannot be used directly for water fluoridation.

According to fluoridation proponent John Small, Alcoa has not sold sodium fluoride since 1952. Some smaller companies market sodium fluoride for various purposes, but, among chemicals, it is the third choice for fluoridation in the United States. Furthermore, the U.S. aluminum industry is a major consumer of fluosilicic acid, the chemical most often used in water fluoridation. Thus, the aluminum industry might actually benefit financially if water-supply authorities were not competing for supplies. Finally, sodium fluoride was never a waste product from aluminum manufacturing, but had to be produced separately. According to this evidence, the view that aluminum companies gain financially from sales of fluoride wastes has never had much basis.

Today, most fluoride for community water fluoridation in the United States comes from fertilizer companies. For them, fluoride is a waste product. Antifluoridationists can claim that fertilizer companies have a vested financial interest in fluoridation. A letter from an official of the federal Environmental Protection Agency spells out the connection clearly.

But this argument is limited by the fact that fertilizer companies make only a small part of their profit from selling fluoride wastes.

Wendy Varney has elaborated on the more sophisticated argument that aluminum and fertilizer companies mainly benefit from fluoridation not through sales of fluoride but through an altered public perception of its toxicity. Before fluoridation, fluoride was something to avoid if at all possible. But with the push for fluoridation, fluoride became touted as beneficial and as something that people need to have.

In other words, the existence of fluoridation does not change the toxicity of fluoride wastes from aluminum smelters and fertilizer factories, but it may well change the public perception of those wastes. It might be more difficult to win lawsuits against companies for fluoride pollution if fluoride is constantly proclaimed as a great boon to humanity. Likewise, it might become easier to argue for dumping of fluoride waste or the construction of new plants if fluoride has a good public image. Fluoridation, according to this argument, provides significant symbolic benefits for the aluminum and fertilizer industries, and these symbolic benefits can translate into financial benefits.

This argument is harder to dismiss outright, but it also needs more evidence to be convincing. It made more sense in the early years of the promotion of fluoridation and
before the rise of the environmental movement. Since the 1960s, the public has been increasingly attuned to the hazards of environmental chemicals. In this context, it may be more accurate to say that industrial fluoride pollution hurts the cause of water fluoridation than to say that fluoridation does much good for industrial fluoride polluters.¹²

The second strand of the argument that aluminum companies are implicated in the promotion of fluoridation is that there are direct links between the companies and promotion of fluoridation. This evidence dates mostly from the 1940s, in the period before the major endorsements of fluoridation. As noted earlier in this chapter, Gerald Cox is one link between aluminum companies and fluoridation, via the Mellon Institute. Another link is Oscar Ewing, an attorney, who was employed by the Aluminum Company of America in 1944 at a salary stated to be $750,000.¹³ Ewing then stepped down to become the Federal Security Administrator, a position putting him in charge of the USPHS. During his time in this position, the USPHS endorsed fluoridation in 1950. Another connection is that Andrew Mellon, founder of Alcoa, had earlier been Treasurer of the United States, at a time when the USPHS was part of the Department of the Treasury.

Do such connections show that aluminum interests were behind fluoridation? By themselves, the roles of these individuals suggest the possibility that fluoridation was seen as compatible with the interests of aluminum companies. But whether this evidence is convincing or not is likely to depend on a person’s view about fluoridation. The evidence would hardly seem to be enough to show to everyone — as it does to Waldbott, Burgstahler, and McKinney — that “Industry’s vital role in promoting fluoridation cannot be doubted nor can the leadership of ALCOA be denied in this affair.”¹⁴

It is recognized, even by antifluoridationists, that aluminum companies have not played any substantial visible role in the promotion of fluoridation since the 1940s. Furthermore, there is little evidence that fertilizer companies have ever played an overt role. The claim is that they were implicated in the early stages of promotion — which got it going in the first place — and that, since then, the companies have left the running to others. This is a weak formulation of corporate influence in fluoridation, and hardly different from saying that they have never been active promoters but, perhaps, have been passive beneficiaries of fluoridation campaigns.

**SUGARY FOOD COMPANIES**

Sugar and sugary foods are widely recognized by dietary specialists and the public alike as responsible for tooth decay. It is in the interests of corporations that manufacture and sell sugary foods to minimize the impact of this problem on their sales and profits. There are various ways to do this. Blaming people for not brushing after every meal or snack is one example. But there are limits to this approach, especially since people do not like to blame themselves when they or their children suffer excruciating toothaches.

Another approach is to find some other way to reduce tooth decay, with “other” referring to any way that doesn’t involve less consumption of sugary foods. Sugary-food interests have funded research in a variety of areas, including the search for a vaccine against caries and the search for “protective factors” in foods that might naturally prevent decay.

Fluoride is, in many ways, the ideal solution from the point of view of sugary-food interests. It is something to be added to the diet; therefore, attention is drawn away from the decay-producing characteristics of sugar. It is paid for by the consumer or the community, either in the form of individual purchases of fluoride tablets or fluoride toothpastes or in the form of community-wide provision of fluoridated water. Finally, the impact of fluoride on decay is considered to be large.

The point is that decay, instead of being perceived as caused by sugar in the diet, is seen as due to a deficiency of fluoride. Indeed, promoters of fluoridation frequently talk about “fluoride-deficient waters.”

The manufacturers of sugary foods have no direct financial interest in fluoride products,
but there is an obvious indirect benefit. If campaigns against sugar by dentists, parents, and health groups are diverted, if only in part, by the refocusing of their concerns toward the need for fluoridation, then a potentially serious threat to profits is thereby defused.

There are also some suggestive intermediate links between sugary-food manufacturers and the promotion of fluoridation. In Australia, the Dental Health Education and Research Foundation (DHERF) provides a link between industry and the dental profession. DHERF devotes a significant part of its efforts and funds to the promotion of fluoridation. For example, it spent $40,000 to support fluoridation in a referendum campaign in 1979. Wendy Varney reports that “Donors to, and members of, the Foundation include an array of manufacturers of sweets [candy], biscuits [cookies], soft drinks and cereals: Colonial Sugar Refining Co. Ltd; Australian Council of Soft Drink Manufacturers; Arnott’s Biscuits Pty Ltd; Cadbury Schweppes Pty Ltd; Kellogg (Aust.) Pty Ltd; Scanlens Sweets Pty Ltd.”

Although its stated general objective is to improve dental health education and improve dental research, Varney reports that DHERF has not taken any steps to help restrict the amount of sugary foods in school cafeterias or to put tighter controls on advertising of food on children’s television programs, two areas where there has been considerable activity by groups of concerned parents and citizens. DHERF thus appears to embody the interest of sugary-food manufacturers in promoting fluoridation as a preferred option for combating tooth decay.

Similar to but less focused than DHERF is the American Council on Science and Health (ACSH), which describes itself as “a national consumer education association directed and advised by a panel of scientists from a variety of disciplines. ACSH is committed to providing consumers with scientifically balanced evaluations of issues relating to food, chemicals, the environment and health.” ACSH is heavily supported by corporate donors, including many manufacturers of sugary foods. It prepares reports on a wide variety of topics — such as cancer, fast foods, cigarette smoking, alcohol, pesticides, and saccharin — almost always taking a position congenial to corporate interests. Its report on fluoridation is strongly supportive. Also, some of the members of ACSH’s Board of scientific advisors — such as Stephen Barrett and Sheldon Rovin — are ardent fluoridation proponents.

There are also a number of individual researchers who seem to serve the interests of sugary-food manufacturers in a similar manner to DHERF and ACSH. Some leading proponents of fluoridation — including Frederick J. Stare at Harvard University, and Elsdon Storey at the University of Melbourne — have received large research grants from sugar interests. In addition, Stare has been one of the seven members of the Board of Directors of ACSH. This is compatible with the idea that sugary-food interests believe they benefit from the promotion of fluoridation.

For sugary-food manufacturers, fluoridation provides little or no direct benefit. But there are very large indirect benefits, which arise by diverting potentially damaging attacks from consumer interests into the promotion of fluoridation or, indeed, into the debate over fluoridation. In addition to this general argument, there is some evidence of corporate research contributions to researchers and organizations that promote fluoridation.

**TOOTHPASTE COMPANIES**

Most toothpastes today contain fluoride. Superficially, it would seem that water fluoridation would not be in the interest of toothpaste manufacturers, since, if tooth decay is prevented by fluoridation, people would have no need for toothpaste. Indeed, some promoters of fluoridation argue that brushing the teeth has no demonstrated benefit so far as tooth decay is concerned — aside from fluoride in the toothpaste — although it is important to prevent the serious problem of gum disease.

As in the case of aluminum and sugary-food manufacturers, the benefits of fluoridation for toothpaste manufacturers are indirect and symbolic. If fluoride is widely perceived
as beneficial, and if people are aware that toothpastes contain fluoride, then they are more likely to buy fluoride toothpastes. This has been a successful marketing strategy, especially since the American Dental Association’s 1960 endorsement of Crest, a toothpaste produced by Procter and Gamble. US sales of Crest dramatically rose after the announcement of this endorsement and its use in advertising. Other toothpaste manufacturers have seen the necessity to include fluoride in their product. The only exceptions are some manufacturers of fluoride-free toothpastes catering to the minority of people actively trying to avoid fluorides.

Toothpaste manufacturers have supported a favorable image for fluorides. For example, a representative of Colgate-Palmolive is one of the six governors of DHERF. Although there has been some friction between promoters of water fluoridation and fluoride toothpastes, they seem to support each other today, or at least do little that is hostile.

There are also some other industrial interests with a stake in a favorable image for fluoride, notably pharmaceutical manufacturers that produce fluoride tablets and other industries that produce fluoride waste. But it is the aluminum, fertilizer, sugary-food, and toothpaste manufacturers that are most affected by the image of fluoride, while the sugary-food and toothpaste industries have been the most prominent in providing funds to investigate fluoride and to promote fluoridation. This provides the basis for the claim that industrial interests are “behind” fluoridation.

**Capitalism and the Dental Profession’s Promotion of Fluoridation**

Although manufacturers of aluminum, fertilizer, sugary foods, and fluoridated toothpaste have an interest in a favorable image for fluoride, there is still only relatively limited evidence that these companies have been directly involved in promoting fluoridation. As described in previous chapters, it has been the dental profession and research scientists — or more precisely a minority of activists within these groups — who have been the driving force behind fluoridation. How can the alleged influence of profits be accommodated to the central role of the dental profession?

One way to look at the problem is in terms of “alternative paths” for the dental profession. In the 1940s, there were several directions the dental profession might have taken to deal with the problem of tooth decay. These included:

1. Promoting fluoridation of public water supplies;
2. Promoting voluntary uses of fluoride such as tablets, toothpastes, and topical treatments;
3. Emphasizing oral hygiene;
4. Mounting a continuing campaign to limit easy access to sugary foods; and
5. Promoting voluntary restrictions on eating sugary foods.

In practice, some dentists have been involved in each of these areas. Nevertheless, there have been differences in emphasis. Fluoridation has been tackled much more vigorously than has limiting access to sugary foods. Why have some directions been pursued more strongly than others?

My hypothesis is that dentists collectively have moved along a path bounded by at least three sometimes conflicting aims: improving the dental health of the population, protecting the interests of the dental profession, and avoiding major conflict with powerful groups.

I have already described how fluoridation can be interpreted as a measure adding status to the dental profession while not substantially threatening the jobs of dentists. The added point, in this instance, is the aim of avoiding conflict with powerful groups.

Promotion of fluorides does not put the dental profession in conflict with any powerful interest group. The aluminum and fertilizer industries, even if they are not much involved in promoting fluoridation, certainly have nothing to lose by the measure. The manufacturers of foods that promote tooth decay are more crucial, however. They are a powerful interest group that would be greatly threatened.
by a major and continuing campaign to provide controls over eating habits. By not confronting these industries in a major way, but, instead, promoting fluoridation or just promoting individualistic steps to better oral health, the dental profession has taken a path of less resistance.

In the light of the massive resistance to fluoridation in numerous countries, it may seem that the profession has not really taken an easy path. But the opposition to fluoridation has provided relatively little threat to the status of dentists, especially as the profession has been able to paint opponents as cranks. The opponents have included only a few individuals of great standing, and are backed by little money or influence. This contrasts greatly with what the food industry might organize against dentists should it be so inclined.

Imagine a different scenario, in which the dental profession led a campaign to outlaw the sales of foods with added sugar, or to penalize the sales of refined carbohydrates by crippling taxes. By analogy to fluoridation, the policy of "nonsugarization" could be justified by demonstrated benefits of improved dental health, and improved physical health as well. Under such a policy, it would still be possible to obtain sugary foods, just highly inconvenient, much as it is highly inconvenient to obtain fluoride-free water where water supplies are fluoridated. One could develop a close analogy between fluoridation and nonsugarization. For example, nonsugarization could be portrayed as ensuring that members of all social groups receive an optimally nutritious diet, the same way fluoridation is portrayed as providing an optimal level of fluoride for dental health.

The arguments about freedom of choice are potent ones against a policy of nonsugarization. People should have the right to choose the food they eat, even if it is not always the best for them. This argument is not fundamentally different from the freedom-of-choice argument against fluoridation. But there is a basic difference in the circumstances. That difference is the food industry, a massive industrial interest promoting selling refined carbohydrates and opposing nonsugarization. Meanwhile, there is no substantial industrial or other powerful interest opposing fluoridation.

The very idea of enforced nonsugarization probably sounds ludicrous to most people, precisely because the concept of consumer choice is promoted so heavily — although mostly implicitly — through the market system and through advertising. Most people believe they have every right to buy sugary foods, and any suggestion to the contrary is dismissed as heavy-handed interference. My argument is that the logic of this is similar to the logic of the case against fluoridation. The difference in people’s responses is due to the vastly different array of interest groups involved, and the way in which perceptions of acceptability have been shaped over the years.

Arguably, the dental profession unconsciously took a path of lower resistance in promoting fluoridation rather than nonsugarization, precisely because of the difference in powerful interests likely to oppose these policies. This is not to say that the profession took a "wrong" path. It is possible that a path of less resistance also achieves more in the circumstances shaping the paths. But it cannot be said, if we accept this analysis, that the profession’s path was one shaped entirely by scientific evidence and concern for dental health. An unconscious accommodation to vested interests seems also to have been important.

So, according to this perspective, two factors explain the continuing commitment to fluoridation by dental elites and most dentists. One is the profession’s investment of its own credibility in the measure. Rejecting fluoridation would mean losing a lot of face and admitting culpability for imposing a risk on the public. The second factor is the continuing power of the manufacturers of refined carbohydrates, which make a major challenge to commercial interests in current dietary patterns into a risky and difficult venture for dentists.

Although this explanation may seem plausible for capitalist countries, it has difficulties in explaining the introduction of fluoridation in communist countries where the selling of refined foods is not linked to profit. Whether bureaucratic imperatives shape the
decision-making context in a fashion similar to capitalist societies in this area is, to my knowledge, completely unexplored.

**INTERESTS AND SCIENTIFIC KNOWLEDGE**

Corporate interests have influenced the role of scientific knowledge in the fluoridation debate in several ways. Most directly, corporate funding of research in particular areas — such as fluoride toothpastes — has led to results that are taken up in the debate. Just as importantly, the failure of corporations to fund more research in particular areas than they actually do — such as on diet and tooth decay — means that certain kinds of results are not available to be taken up in the fluoridation debate. Some corporations have directly or indirectly supported partisan activity in the fluoridation struggle. Finally, corporations, by their presence and potential for action, have provided part of the political environment that encouraged the dental profession’s emphasis on fluoridation as a method for combating tooth decay.

In this chapter, I have focused on the role of corporate interests in the fluoridation controversy. Other areas also deserve attention.

The state (government and related institutions), which has played a key role in decision making about fluoridation, has received some consideration from analysts. The legal system deserves further analysis. There has been very little comparative analysis of the dynamics of the fluoridation controversy in different countries as a function of different social and political structures.

The role of patriarchy has also been unexplored and unmentioned. Whereas most leaders of the dental profession — and most leading promoters and opponents of fluoridation — have been men, women have usually taken the greatest responsibility for the oral hygiene and diet of their children.

The significance of this and other gender-related differences remains to be studied. The ways in which the state, the legal system, the national political structure, and patriarchy have shaped the struggles over scientific knowledge in the fluoridation debate remain to be studied.

**NOTES**


2. Ibid.

3. It might be argued that antifluoridationists have an interest in freedom of choice and in opposing the coercion of compulsory mass medication. Here, I set this aside and concentrate on interests such as money, power, and prestige. One difficulty is that noble values, such as freedom, often serve to legitimate more sordid interests, in the same way that “freedom” in capitalist societies is often a mask for corporate power and “peace” in Communist societies involves support for government military policies. Beliefs in values such as peace and freedom may be quite sincere and influential, but analysis of interests concentrates on material factors influencing people’s actions.


5. See, for example, articles reprinted in *Cancer Control Journal*, vol. 5, nos. 1 and 2 (1978): 75-80.


8. Waldbott et al., op. cit., 305.

9. Ibid., 312; and Varney, op. cit., 59.


12. I thank Mark Diesendorf and Edward Groth III for comments in relation to this point.


14. Waldbott et al., op. cit., 313.


18. Another path not taken is the promotion of “complete tooth nutrition,” which involves ingesting a variety of key minerals and vitamins during childhood. See Alfred Aslander, “The Theory of Complete Tooth Nutrition as a Natural and Effective Dental Caries Prophylaxis,” *Journal of Applied Nutrition*, vol. 17 (1964): 190-204. I thank Albert Burgstahler for making this point.


Making a decision

How should — or could — a decision be made about fluoridation? If science is not a solution, neither is politics. There is no political system free from the inherent difficulties of decision making when claims of scientific knowledge are disputed and issues involve both scientific and political dimensions.

The foregoing chapters have shown several ways to examine the debate. At the level of ideas and arguments, there are ongoing disagreements and disputes over the evidence about the benefits and risks of fluoridation, and the relation of fluoridation to human rights. In the minds of the leading partisans on the issue, the arguments are tied together into unified assemblages, which serve either to support or oppose fluoridation. What we have is not a disparate set of arguments, but rather two different pictures of the world. Each side tries to win adherents to its own coherent picture.

Evidence, logical arguments, and emotional appeals are involved in the case presented by each side. But the struggle goes beyond this into attacks on the credibility of those on the other side claiming to be experts. To establish authority, both in the relevant professional communities and the wider political scene, soundness of evidence and argument apparently is not seen as sufficient. Credentials and authoritative bodies are trotted out whenever possible, and the credibility of those on the other side is belittled, both subtly and blatantly. Of importance here is the circulation of dossiers of derogatory comments.

There is also the more direct use of power, notably the mobilization of the resources of the dental profession on occasion to attack opponents by expelling members from dental associations, denying publication, and blocking research funds. When the dental profession has been captured by profluoridationists, then all available professional power may be brought to bear against vocal dissidents.

Finally, there is the overall political and economic context of the debate, especially with relevant corporations and the state. These can influence the direction of initiatives within the dental profession by making some strategies for tackling dental decay more feasible and attractive. Rather than directly confronting corporate interests, it may seem more natural or sensible to deal with the problem by another route.

Do these perspectives provide any insight into what should be done about fluoridation or, without committing oneself to a particular stance, how a decision should be made?

Fluoridation and democracy

Some social scientists, examining the bitter struggle, have concluded that democracy is an inappropriate decision-making procedure for dealing with public health issues such as fluoridation. Harvey Sapolsky, a political scientist at the Massachusetts Institute of Technology, wrote in 1968 that “The experience with fluoridation seems to confirm the inappropriateness of direct citizen involvement in policy-making.”

Sapolsky assumes that a rational, scientific evaluation shows the safety and benefits of fluoridation, and contrasts this to citizen opposition. He concludes that democracy, in the sense of citizens being involved in social decision making, is incompatible with scientific advancement in society. His solution is the familiar one of representative democracy in which the citizens choose political leaders, who then evaluate the measure by using expert advice.

Donald McNeil, historian and long-time supporter of fluoridation, takes a similar stance. He states, “It would be reassuring if elected officials could dispassionately weigh the factual information on fluoridation, then
Making a decision

...calmly make the decision, with the public abiding by the overwhelming body of scientific evidence that fluoridation is effective, efficient, inexpensive and safe." He considers that the continuation of the fluoridation controversy, rather than the complete implementation of fluoridation, is a price that Americans pay for their open political system.

The trouble with these formulations is that they draw conclusions about citizen participation on the basis of a presumption that the scientific case for fluoridation is conclusive. Profluoridationist Russell Scobie, who is opposed to referendums on fluoridation, encapsulates this assumption in his statement that "A referendum cannot establish or destroy a scientific fact." This view is flawed in two ways. First, it ignores or dismisses the scientific criticisms of fluoridation. Second, it assumes that fluoridation is strictly a scientific issue, whereas actually it has crucial ethical and political dimensions.

A preference for decision making by elected representatives is convenient for supporters of fluoridation in the United States because, on the basis of experience there, public officials are easier to convert to fluoridation than is the general public at a referendum. Yet, a look at decision-making procedures elsewhere in the world casts doubt on this view: in countries more open to citizen involvement, with more frequent referendums and decision making by local government units, there is usually a higher implementation of fluoridation. This includes Australia, Canada, New Zealand, and the United States. In liberal democratic societies where administrators and politicians at the national level have more sway — notably in a number of European countries — there is little or no fluoridation. As mentioned in chapter 3, there are a number of possible explanations for the lack of fluoridation in Europe, and research to test these explanations remains to be done.

Most debates about decision-making procedures over fluoridation are really part of the debate over fluoridation itself. It is no coincidence that proponents support, at least in principle, decision-making methods that they think will lead to fluoridation, and, similarly, that opponents support methods they think will allow it to be stopped.

**DECISION-MAKING STRUCTURES**

There is a considerable literature concerning decision making on science policy and indeed quite a lot on the ways fluoridation decisions are made. Almost none of this, though, confronts the implications of a struggle for credibility and using all available resources at the level of scientific knowledge. Rather than deal with the full range of issues concerning decision making — including everything from campaigning techniques to the politics of science policy — I have a limited objective here. I examine several contrasting political systems to determine whether any of them provides a way of handling the fluoridation controversy by addressing the problems raised by struggles over the production, assessment, and credibility of scientific knowledge claims.

**DICTATORSHIP** is a political system based on rule by a single person or, by extension, a small group. Once a dictator has made a decision, it is supposed to be implemented throughout the society. A dictator can be benevolent, malevolent or, more likely, a combination. For the sake of argument, let us assume that the dictator considering fluoridation is benevolent, and desires the greatest good for the greatest number of the people, aside from political participation. On the surface, the dictator can simply examine the evidence and arguments and make a decision.

But this does not solve the problem, for, unless the dictator is also the world’s foremost scholar on all aspects of fluoridation, the dictator has to rely on advice. This could be from dentists, epidemiologists, political advisors, ethicists, economists, or secret police. The point is that the system of dictatorship does not resolve the issue because the struggle over fluoridation will take place at the level of advisors. The people who make the presentation and the particular evidence and arguments presented to the dictator will shape the decision.

In the modern world, however, classical dictatorships are rare.
BUREAUCRATIC STATES, in which a system of government bureaucracies makes key administrative decisions with little outside input, are more common. The bureaucratic state characterizes much about communist societies and, as well, quite a lot about capitalist societies. Once again, let us assume for the sake of argument that the relevant health bureaucracy is benevolent, seeking to maximize community welfare in a way that is compatible with continued maintenance of the bureaucracy itself. In the bureaucratic system, outside pressure groups such as dentists, environmentalists, or defenders of individual rights have little access to the corridors of power.

It might seem that the bureaucrats could simply listen to all relevant experts and representatives of interest groups, make a decision, and implement it subject, of course, to convincing their nominal political masters. But bureaucracies are not exempt from power struggles. Indeed, a bureaucracy can be considered to be a type of political system, in which various groups struggle within the organization’s hierarchy, division of labor, and regular routines to implement measures cementing their own positions within it. Bureaucracies commonly have an “old guard” committed to long-established policies. Young rebels challenge the status quo, not only because they believe in different ways of doing things, but also because this is a way to advance their careers.

If the issue of fluoridation had been left entirely to bureaucratic states, it is quite likely that it would never have gotten underway in the first place. Remember that, in the 1940s, the USPHS was resistant to premature promotion of fluoridation, and succumbed only to an impassioned and effective lobbying process coming partly from the outside. In a more bureaucratized state, the energy of the dentists from Wisconsin might never have succeeded against entrenched conservatism. Communist bureaucracies have investigated and implemented fluoridation only after it was widely promoted in many other countries, especially those with more pluralist political systems.

TECHNOCRACY or direct rule by experts is another option. In practical terms, this might mean that a decision on fluoridation would be reached by a panel of experts or an expert inquiry with executive powers. Technocracy sounds attractive to some scientists and other experts, but, in practice, it degenerates into a type of dictatorship or bureaucratic state. Those experts who take on the role of decision making must inevitably deal with issues outside their immediate range of expertise, and this process leads quickly to a more bureaucratic role. Furthermore, the structure of a technocracy demands an answer to the question of who are the real experts. The answer, in practice, will depend on a struggle for power.

REPRESENTATIVE DEMOCRACY is based on election of representatives who have formal decision-making power. In pluralist systems with elections and political parties, representatives are subject to pressure from a range of interest groups, including constituents, lobbyists, government bureaucrats, political party officials, and the media. The wide range of pressures means that there can be no preordained conclusion on fluoridation. The intense activity by both profluoridationists and antifluoridationists in systems with elected representatives testifies to their belief that political mobilization is crucial, and the political system does not automatically lead to any one decision.

This applies even when legislators set up a committee to hear testimony from experts and citizens, and then make a judgment. In practice, such committees have served as one more forum for the continuation of the fluoridation debate, rather than as a method for resolving it.

REFERENDUM is another system. Suppose, for the sake of argument, that all fluoridation decisions are implemented without question on the basis of a majority vote by people in a given public water supply area. Whatever conditions are imagined, this would still allow the losing sides to dispute the result as unfair.

There can be disputes about the wording of the referendum and disputes about resources available for informing the public. For
example, one side or the other might claim that only those with certain types of education can fully understand some of the evidence; therefore, the education system may influence the result. Factors of gender, ethnicity, class, and geography could also play a role. Almost always, there will be a disgruntled minority, some of whom may decide that pressure group tactics are warranted in the case of defeat at the referendum. Thus there is no guaranteed conclusion to the controversy.

UNANIMITY is another decision-making procedure. Everyone must agree before a decision is made and implemented. This is feasible only in small communities. As a decision-making procedure, unanimity gives incredible power to the status quo.

CONSENSUS is a modified system in which all that is required is that no one strongly objects. Some may disagree but not feel sufficiently strong about it to seek to block the group’s action. Consensus, in this sense, has been used considerably in collectives of various sorts, and is the implicit method in settings, such as the New England town meeting, where voting is the formal system. Under consensus, a single strenuous objector to fluoridation could stop its implementation or, if fluoridation were already introduced, a single objector could keep it from being removed. Consensus systems usually lead to an intense effort to find a solution satisfying everyone. For example, a possible resolution would be to fluoridate the public water supply but provide free unfluoridated bottled drinking water to anyone who wished to have it.9

Consensus systems have their own power struggles. Because the decision-making process is open — rather than the secret ballot common in elections — the pressure on dissenters to conform in order to reach a decision can be intense.

In any of these systems — from dictatorship to consensus — the role of economic structures and interests, as well as other groups such as professions, should not be forgotten. Corporate and professional interests may be crucial in putting fluoridation on the political agenda rather than some other issue relating to dental health.

Even without this caveat about wider structures, it appears from this brief survey of political systems that there is no neat resolution available of the fluoridation issue. The debate over fluoridation includes a political struggle, and no political system is exempt from such struggle. Only the form of struggle — and the likely outcome in different historical circumstances — is different.

Some of the participants in the debate may pine for a system in which the issues are dealt with logically and clearly, and a decision is made and then implemented in a clear, sensible, and effective manner. Any system alleging to do this would be papering over a multitude of problems, conflicts, and commitments.

Looking through the literature on political philosophies — whether liberalism, Marxism, or anarchism — it is remarkable how little help is provided in dealing with controversies such as fluoridation. The problem is that disputes over scientific knowledge are intertwined with disputes over values. They also become involved with wider power struggles, and traditional political philosophy assumes that claims of scientific knowledge can be unambiguously adjudicated in a realm of science separate from ethics and politics.

Arguably, science is always inherently bound up with systems of power.10 But, even short of this claim, it is certainly the case that science related to fluoridation is carried out in a situation where knowledge is entwined with power struggles. The traditional assumption that adjudication of claims based on scientific knowledge is separate from social decision making does not hold true. A minimum response is the open recognition of this situation, so that social claims are less able to disguise themselves as claims about scientific knowledge.

In order to have credibility throughout the community, a decision-making method should be able to deal simultaneously with both the technical and value aspects of any issue in a way that reflects both the interests and values of the entire affected community. The trouble
with systems that put elites and experts in crucial decision-making roles is that the interests of the elites and experts themselves are likely to intrude.

Elections provide far too indirect a connection with community concerns, and politicians are notoriously susceptible to pressure groups. The more populist alternative of referendums also has a crucial shortcoming: most people do not have the time to study all the arguments of fluoridation — not to mention all sorts of other controversial issues — and, hence, referendums often become political carnivals. Therefore, it is worthwhile to focus more closely on methods that involve a group of people making a careful assessment of the issues. This includes formal inquiries, the science court, and the citizens court, among others.  

The fluoridation issue has two features that make most decision-making methods of this type inadequate or inappropriate. First, the facts are inseparable from values. This is apparent, for example, in the coherency of viewpoints across technical, ethical, and political issues. Any method that assumes or requires a separation of facts and values will be unable to deal satisfactorily with the issue. The proposed science court — which relies on a panel of neutral experts hearing testimony and adjudicating factual matters only — falls into this category.

Second, there are almost no experts who are not identified with one side or the other. The tremendous polarization of viewpoints means that there is hardly anyone having credibility with both proponents and opponents. Any decision-making methods that include experts — such as a science hearings panel composed of both scientists and lay people — can readily be accused of bias on two counts. First, the scientists may have commitments, professional affiliations, or friendships that jeopardize their appearance of objectivity. Second, the members of a science hearings panel are appointed, and those making the appointments can be accused of bias.

These same objections also apply to many prominent laypeople, and this limits the value of a citizen court relying on appointed lay individuals. Similarly, formal inquiries, whether conducted by judges or others, require appointments to be made in the polarized situation.

One approach that has the potential to overcome both these difficulties is the “policy jury.” A group of individuals is selected randomly from the relevant community, making sure to obtain a statistically representative sample by sex, age, and other criteria. This group acts as either a decision-making body or an advisory body. The group listens to, examines, and discusses evidence, arguments, and submissions on all aspects of the issue, both technical and ethical. It is backed up by research and secretarial assistance.

The advantages of the policy jury are that those chosen are unlikely to have any vested interest in the outcome. They are representative of the community, yet have the time to examine the nominated issue in depth. Finally, there is no pretense that scientific issues can be separated from value aspects.

Policy juries have been run in Minnesota on several controversial topics, including the effect of agriculture on water quality and a proposal to introduce school-based clinics to deal with teenage pregnancies and sexually transmitted diseases. The randomly selected jurors have taken their roles extremely seriously, shown a good grasp of the issues, and evaluated the jury process very positively. The results of these jury deliberations have been received favorably by both the media and politicians.  

Similar exercises have been carried out in West Germany. “Planning cells,” which are groups of randomly selected citizens, have dealt with issues such as energy policy, town planning, and information technology.  

I believe that the policy jury or planning cell is one of the few decision-making methods with the potential to deal with the fluoridation issue in a widely credible way. But it will not satisfy those who believe nonspecialists cannot nor should be making judgments about issues with a significant technical component.
CLOSING THE DEBATE

Let us turn now from how the debate in principle should be resolved to possible reasons why the debate might actually be closed in the future. If the key to the debate is struggle using a range of resources from rhetoric to professional power, then changes in the available resources can readily change the state of the debate.

One way long-standing debates fade away is through gradual withdrawal or death of leading advocates on one side. For example, some physicists did not accept the innovation of relativity in the early 1900s. But this “old guard,” never very strong, became less vocal and its leading figures eventually died.

The fluoridation debate has gone on for well over a generation. Many of the original partisans have died or withdrawn. Professor J. D. Jackson, a leading advocate in Britain, died in 1987. George Waldbott, the leading opponent in the United States for many years, died in 1982, and Dean Burk died in 1988. But new partisans have stepped into the breach on both sides, such as proponent Brian Burt and opponent John Lee. There is little evidence that either proponents or opponents are failing to attract new adherents. In other words, the debate is not fading away as an “old guard” withers on the vine.

Because only a minority of dentists, doctors, and scientists openly oppose fluoridation, the antifluoridationists are more vulnerable to the loss of a few key individuals. On the other hand, they continue to attract considerable popular support, and there is a sufficient body of scientific literature to maintain activism even without many active experts.

Another way the debate could be transformed is through switches of allegiance. On an issue as highly polarized as fluoridation, the defection of a few prominent figures can be extremely influential. The best example here is John Colquhoun’s change of opinion.

Colquhoun supported fluoridation throughout most of his career, in which he rose to become Principal Dental Officer of Auckland, New Zealand. He went on a world tour shortly before retirement to examine the case for fluoridation, and ended up deciding against it. Since 1984, he has been one of the world’s leading opponents. Changes of position of this sort are especially effective because the individual has an intimate knowledge of the other side in a way no active partisan would be offered.

Colquhoun’s switch of allegiance, while very damaging to proponents, was not as significant as it would have been if he had earlier been a more highly prominent proponent. Indeed, it is hard to find a single example of a leading partisan who has switched sides. They are much more likely to drop out of the debate entirely.

Another way in which the balance of power in the debate might change is through new issues and new supporters. This possibility arose in 1987 with a brief report in the prestigious scientific journal *Nature* that, when water boiled in aluminum pots was fluoridated, a much greater concentration of aluminum entered the water than when the water was unfluoridated. In other words, it was suggested that fluoridated water was leading to much higher intakes of aluminum. This was seen as significant because some scientists have linked aluminum intake to Alzheimer’s disease, which involves degeneration of brain connections and is said to be widespread especially among the elderly.

If this report had been replicated and vindicated and the aluminum-Alzheimer’s connection shown more conclusively, it might have brought a new constituency into the fluoridation debate, that of doctors and citizens concerned about Alzheimer’s. The solution would not necessarily have meant ending fluoridation, since it is also possible to replace aluminum pans, but this example shows, nevertheless, the potential for mobilizing new supporters. As it turned out, the reported results were refuted and retracted, a result readily accepted by antifluoridation scientists such as Albert Burgstahler and Mark Diesendorf. Burgstahler carried out the experiment himself and found no unusual aluminum leaching. But this was not before many antifluoridationists had proclaimed that the initial findings vindicated their opposition.
Fluoridation proponents have tried to expand their constituency through a connection between fluoride and the disease osteoporosis. In osteoporosis, the bones become porous and prone to breakage, a problem especially likely to affect postmenopausal women. The usually recommended antidotes are estrogen replacement therapy, calcium supplements, and regular exercise.

Another approach is heavy doses of fluoride. Not surprisingly, this method is touted by profluoridationists. There have been a few studies showing that fractures in the elderly are less common in regions with fluoridated water,\(^\text{19}\) and other studies contesting this correlation.\(^\text{20}\) If profluoridationists can convince people that fluoridation helps to reduce the incidence of osteoporosis, this would attract a new constituency to the cause of fluoridation. So far this has failed to occur.

Convincing new constituencies of a striking new risk or benefit of fluoridation has the potential to change the balance of the debate dramatically. The best example of this effect is the claims about fluoridation and cancer presented by Yiamouyiannis and Burk, which greatly helped the opponents in the 1970s. Note that claims do not have to be scientifically correct in order to be persuasive. The claims about fluoridation and cancer were effective politically even though many scientific refutations were published. Similarly, profluoridationists have made claims for decades about the beneficial effects of fluoridation for bones without much scientific backing, although, in this case, the benefit for the fluoridation cause has not been great.

The most important potentially new constituency in the debate is the environmental movement, which could put fluoridation on its agenda as a form of pollution and a health hazard. So far, this has happened only to a limited extent, with some individuals, such as Ralph Nader, and organizations openly opposing fluoridation. Mainstream environmental groups have not adopted the antifluoridation cause. If this were to occur, it would shift the balance in the debate.

Edward Groth III has been watching the debate for decades, and he does not expect any sudden change in the balance of power. He believes “the balance is like a limestone formation in a cave; each new study or recruit is like a drop of water that leaves a tiny residue, and the mass of evidence and informed people gradually grows on the anti side. On the pro side, political victories and recruits are also piling up slowly. If the balance eventually is shifted, it will probably not be catastrophic, but gradual, and not necessarily centered on any one event or new research report.”\(^\text{21}\)

**SIDESTEPPING THE DEBATE**

There are several other scenarios in which the fluoridation debate is not resolved but, instead, becomes irrelevant. A decline in tooth decay so that it becomes a rare problem is one way in which this could happen. The declines recorded in industrialized countries — both fluoridated and unfluoridated — over the past few decades already hold the possibility for ending the debate, except that the cause for the decline is disputed.\(^\text{22}\) As long as the decline can be attributed in substantial part to fluoridation, the debate can continue.

On the other hand, if decay were virtually eliminated by some other means, the fluoridation issue would become irrelevant. One unlikely possibility is that the diet for young people would become very wholesome, without the refined carbohydrates that lead to decay.

Another possibility is that an alternative “technical fix” for tooth decay could be developed. One area of study is the use of casein and other compounds found in natural foods, such as milk and cheese, and which reduce decay, as additives to other foods such as candy.\(^\text{23}\)

Another area being studied is vaccines against decay.\(^\text{24}\) If either of these came up with a solution recognized as effective, then fluoridation might be rendered unnecessary.

The reduction in tooth decay provides a way to sidestep the debate, because neither side needs to admit it was wrong. Proponents can continue to insist that fluoridation was needed in earlier years, and that it is only with
the widespread use of fluoride toothpastes, better oral hygiene, and perhaps other unknown factors, that water fluoridation has become less urgent. Opponents can continue to make their claims about the hazards and lack of benefits of fluoridation.

**GOOD STRATEGY FOR THE PROPONENTS?**

Using the benefit of hindsight, let me offer a few comments on the strategy used by proponents of fluoridation. The proponents had enormous early success in winning over to their side the key government and professional bodies. This was gradually translated into actual implementation of fluoridation in the United States and some other countries. The credibility of scientists who were opponents was demolished, but continuing opposition came from local communities with little or no open support from dentists and doctors.

The strategy of the proponents can be seen, from an outsider’s point of view, as one of first capturing the key public health and professional organizations and then using the power of these organizations to marginalize opponents and persuade communities. This strategy might have had more difficulties if the push had started later since, with the rise of the environmental movement in the 1960s, new chemicals have been given exceptional scrutiny. But, by this time, the antifluoridationists had been typecast as right-wing cranks. In the succeeding years, the environmental movement, while showing some interest in the issue, has not put fluoridation fully on its agenda.

In spite of the apparent effectiveness of this profluoridation strategy, there has been continued and bitter citizen resistance, backed by a small minority of professionals. This opposition, while lacking the powerful professional standing of the proponents, has been effective politically. The antifluoridation forces have not faded into obscurity as expected by proponents.

Arguably, the massive early push for fluoridation, which brushed skeptics aside, laid the seeds for its own lack of complete victory. The aggressive promotion in the early years, which drew public attention to the issue, ironically also helped stimulate opposition. The resulting polarization has persisted and acted as a “dogged brake” on greater expansion of fluoridation. Perhaps a quieter and less urgent early promotion would have led to greater success in the long run.

It is possible that a different approach to the testing of benefits and risks could have reduced later criticism. The early trials of fluoridated and unfluoridated cities were criticized by Philip Sutton on a number of methodological grounds. One response would have been to invite Sutton and other critics to be consultants in experimental design, thus co-opting their dissent. Instead, Sutton was attacked. In the 1980s, his criticisms returned to plague the profluoridationists through the studies by Colquhoun and Diesendorf.

Similarly, a greater willingness to respond to and work with early critics, such as Frederick Exner and George Waldbott, who claimed there are health hazards from fluoridation, might have moderated the passion of the opposition. One risk in this is that some of the claims of the critics might have been verified. This could have weakened the passion of the promoters.

Bending over backward to respond to scientific criticisms would not necessarily have eliminated the critics, since any experiment, no matter what its protocol and results, can be challenged and explained away. The fluoridation trials comparing the cities of Tiel and Culemborg in the Netherlands and Anglesey and Mon in Britain are much more sophisticated than those criticized by Sutton, but have, nevertheless, come under attack. But responding to scientific criticisms sometimes can serve to restrict areas of disagreement. More willingness to deal with the critics on their own ground might well have mollified some of them and weakened their alignment with citizen antifluoridation groups.

Fluoridation of public water supplies is only one way to get fluoride to people’s teeth. The promotion of water fluoridation has been a mixed success, with nearly complete failure in Western Europe. But fluoride toothpastes have
quietly had almost total victory, in the sense of being widely adopted without significant controversy. The antifluoride campaigners have largely targeted water fluoridation, to a considerable extent, because of its compulsory aspects. If water fluoridation has been the front line of the struggle, the supporters of fluoride against tooth decay have, in effect, been well inside their opponents’ territory, having won over most of the population to fluoride via toothpaste.\textsuperscript{29} In fact, the struggle over water fluoridation can be interpreted as a side issue, which has attracted the bulk of the attention, while the major changes were happening through fluoride toothpastes and oral hygiene.

This can be interpreted either as a highly successful though unintentional strategy for bringing fluoride to teeth, or as a wasteful expenditure of professional effort which could have been better spent in less contentious efforts at education and routine professional care.

**GOOD STRATEGY FOR THE OPPONENTS?**

The opponents have been able to muster an extraordinary degree of popular support through the years, especially when local decisions are involved. This has been in spite of having the open support of only a tiny minority of experts and in the face of the endorsement of fluoridation by most authoritative bodies. As a populist movement, antifluoridationism has been an amazing success, holding back the tide of fluoridation in English-speaking countries and preventing its widespread adoption in Europe.

It is easy to make criticisms of the antifluoridationists. Their campaigning is frequently riddled with numerous gross exaggerations and misleading claims. Certainly sodium fluoride is used as a rat poison, but there are many substances that are harmful in large doses and beneficial in small amounts. The frequent wild statements about the hazards of fluoride can make serious critics wince. Whether or not the exorbitant claims help or hurt the cause of the opponents more than a sober assessment of shortcomings in the evidence for fluoridation is difficult to say.

Hans Moolenburgh, a leader in the campaign against fluoridation in the Netherlands, argues that aggressive techniques — including calling the proponents liars — are effective and necessary.\textsuperscript{30} Arguably though, many thoughtful critics and potential opponents may have been inhibited from voicing or developing their concerns due to a reluctance to appear associated with the extremes of antifluoridation rhetoric.

The cause of the antifluoridationists would have been helped by documentation of hazards by ever more researchers. Waldbott, no doubt, had good reason to be reluctant to expose his patients and files to critics, especially given his experience in being misleadingly exposed by Hornung.\textsuperscript{31} But, if the phenomenon of fluoride intolerance is to be accepted, investigations by many researchers and clinicians, including skeptical ones, is essential. This is the obverse of the shortcoming of the proponents’ campaign in failing to respond to criticisms by the opponents. A careful documentation of intolerance, reproducible by others, would add greatly to the credibility of claims of that particular hazard.

Another problem with the antifluoridation campaign is that it has been almost entirely negative and reactive. The agenda was set by the supporters of fluoridation in the 1940s, and, ever since then, the opponents have been on the defensive. The opponents are against the measure, whether because of concern about hazards or individual rights. It is not so clear what they are for.

Some of them do take the problem of tooth decay seriously, especially those who push for a better diet. Others are concerned about wider issues of fluoride pollution, including by industry. But these other issues can be lost in the passion of the fluoridation debate. Furthermore, by being continually negative and without a prominent positive program, the image of the opponents is also more negative.

The negative side of the opposition is most apparent in the dynamics of fluoridation decision making. When a national or local government moves to make a decision, the opponents mobilize, often impressively. But while the issue is stabilized, either with or
without fluoridation and with little chance of a change, the antifluoridationists are inactive. With some exceptions, they are not conspicuous in ongoing campaigns for better oral hygiene, better diet, protection of civil liberties, or environmentally sound policies for industry.

If more of the opponents were prominent in other campaigns — especially those with a positive angle — their credibility on the fluoridation issue would be greater. The involvement of environmentalists such as Mark Diesendorf, Robert Mann, and Wendy Varney may indicate a change in this direction. If the antifluoridationists can win over mainstream environmental groups to their cause, their campaigning effectiveness will be immensely strengthened. This strategy may be analogous to the winning over of the USPHS, the American Dental Association, and the American Medical Association by the profluoridationists in the late 1940s and early 1950s.

CONCLUSION

Many people like to believe that there is a correct or rational answer to social and political dilemmas. Most of them want to know simply whether fluoridation is right or wrong, rather than spend lots of time studying the issue. Part of the attraction of the belief in scientific objectivity is that science may provide an avenue for determining an answer.

Unfortunately for this black-and-white picture of the world, there is no final arbiter for many issues involving science. Fluoridation is not purely a scientific issue, since it involves considerations of community welfare, economics, individual rights, ethics, and decision making. But even the science of fluoridation is problematical. Judging the scientific evidence on the issue brings in considerations involving the exercise of power, because such considerations have affected the type of research conducted, opportunities for publication, and the credibility of scientists.

Few decision-making methods acknowledge the power struggles going on over scientific knowledge. Yet, there seems to be no political system that can avoid these struggles. In this sense, politics is not a solution to the fluoridation debate, and it is unlikely that any formal method can be used to satisfactorily adjudicate it. The actual closure of the debate is more likely to come through accumulating small successes on one side or the other, or a shifting of the debate to other issues.

A further complication is that the choice of a decision-making method is just as much a part of the struggle over fluoridation as disputes over benefits, risks, and individual rights. Formal assessments by dental authorities usually favor fluoridation. Referendum results, more often than not, oppose it. Those who discuss the pros and cons of different decision-making methods may appear to be just looking for a way to resolve the fluoridation debate. Whether they realize it or not, they have joined the debate itself.

NOTES


9. In a letter to Brian Martin, dated 8 December 1988, Edward Groth III comments that such a compromise is usually opposed both by antifluoridationists — who say people would not go to the trouble of obtaining the unfluoridated water — and by profluoridationists — who do not want to admit there are any legitimate objections to fluoridated water.


11. See, for example, Leonard A. Cole, “Resolving Science Controversies: From Science Court to Science Hearings Panel,” in Goggin, op. cit., 244-261.


25. A good feel for profluoride strategy is given by P. Jean Frazier in “Priorities to Preserve Fluoride Uses: Rationales and Strategies,” *Journal of Public Health Dentistry*, vol. 45, no. 3 (summer 1985): 149-165, and the following reaction papers and discussion on pages 166-179.

26. I thank Edward Groth III for emphasizing this point.


29. Some fluoridation opponents have also attacked fluoride toothpastes and other fluoride products.

30. Moolenburgh, op. cit.

31. See chapter 4.
The fluoridation issue has aroused not only the passions of many people, but also the interest of numerous social scientists. The controversy is an interesting one to study. It has been heated, and it has persisted for decades. It has involved both science and politics, and it has involved an exceptional degree of public participation, especially in the form of referendums. There is much rich material in the controversy for sociologists and political scientists to explore. In this chapter, I will briefly review the main types of social analysis of the fluoridation controversy, with a goal of placing my own analysis in perspective.

PREVIOUS STUDIES

Most social research on fluoridation has assumed that fluoridation is scientifically proven. This assumption is often not even mentioned and certainly never justified by a careful review of the scientific evidence. In many cases, the making of the assumption must be inferred from the type of analysis made of the fluoridation controversy. The main aim of this type of research is to explain why people oppose fluoridation.

One popular approach has been to look for correlations between people’s views on fluoridation and demographic characteristics such as age, education, income, political position, and number of young children. For example, Mausner and Mausner, in one of the earliest prominent studies, found that a smaller fraction of opponents than of proponents had completed high school.

Another demographic finding was that people older than 60 years of age were more likely to oppose fluoridation. This could be due to lower levels of education, to conservatism, or to lack of any personal benefit. People with young children were more likely to favor fluoridation. Antifluoridationist views have also been linked to conservatism through opinion surveys and studies of correlations between votes on different issues.

Although some intriguing demographic correlations with views on fluoridation have been found by some researchers, most have not stood the test of further investigation. For example, Gamson found a more complex relationship between education and attitudes to fluoridation than did the Mausners. Both those respondents with high levels of education and those with very limited education favored fluoridation, whereas those with medium levels of education were more opposed. Likewise, the correlations between political views and views on fluoridation have not stood up.

A basic problem with these sorts of studies is that correlations between education, age, or other variables and attitudes to fluoridation do not, by themselves, explain opposition. In particular, they do not explain the widely noted change in views during debates on fluoridation. Often, opinion polls conducted before fluoridation became an issue show large majorities favoring the measure, but referendum results often show impressive majorities against fluoridation.

The Alienation Hypothesis

Another widely used approach in earlier studies was to look for correlations between opposition to fluoridation and "alienation. Individuals who were alienated from the dominant culture were thought to use opposition to fluoridation to express their frustrations. Antifluoridationism, according to this hypothesis, is essentially a revolt of the powerless who have latched onto fluoridation as a symbol of the impositions put upon them. Support for this hypothesis was obtained by examining antifluoridation literature, undertaking attitude surveys and interviewing antifluoridation leaders.
There are several difficulties with the alienation hypothesis. Attitudes portrayed by antifluoridation leaders in their literature are unlikely to be typical of all those who vote against fluoridation. The surveys of alienation have been limited in size, and even the concept of alienation leaves much to be desired. Finally, the alienation hypothesis, like the demographic approach, cannot explain changes in opinion during referendum campaigns.

The Confusion Hypothesis

A third approach is based upon the concept of “confusion.” The switch in viewpoints during referendum campaigns is attributed to confusion generated by the debate itself. Voters, having been confronted by conflicting claims presented by those who present themselves as experts, take the “safe” route in opposing fluoridation and any possible health risks.

The confusion hypothesis seems to explain the dynamics of the development of antifluoridation concerns, but does not explain why antifluoridationists have been able to mount campaigns in so many cities over so many years. Nor does it explain why antifluoridation campaigns have continued to succeed, whereas similar efforts against pasteurization faded away.

The demographic, alienation, and confusion approaches each assume that supporting fluoridation is rational, namely, in agreement with scientific evidence and a progressive social outlook. Therefore, support for fluoridation does not have to be explained by using social analysis. Because support for fluoridation is rational, opposition then must be irrational in some sense. Therefore, the task of social analysis is to explain the opposition.

Note that these explanations use categories that present opponents of fluoridation in an unflattering light. They are uneducated, alienated, confused, or even just plain irrational. The use of such categories would be unlikely without the assumption that fluoridation is correct.

In addition to the specific shortcomings already mentioned, there are several problems with this general approach, which can be empirical or theoretical. Empirically, it is very hard to explain the lack of fluoridation in Europe and many other countries. In most of these countries, there has been less citizen participation in decision making, and certainly less reliance on referendums than in the United States. The decisions not to fluoridate have, in many cases, been made by government bureaucracies advised by various experts — precisely the groups that, in the United States, have more often supported fluoridation.

No doubt, it would be possible to develop a social explanation of the relative lack of fluoridation in Europe. But such an explanation would have to go beyond the use of demographic correlations and the concepts of alienation and confusion, which are inadequate to the task. It is not surprising that those using these approaches have almost always ignored struggles over fluoridation outside the United States.

On the theoretical side, one difficulty with the assumption that fluoridation is scientifically based is that considerations of ethics and public policy are involved, too. There is the issue of compulsion; the issue that the benefits go to only some sections of the population (none to the toothless, for example); the issue that any risks affect only some sections of the population; the issue that alternatives to water fluoridation will lead to a different distribution of costs and benefits; and the issue of who should make the decision. Those who assume that fluoridation is rational have assumed, in addition to its scientific validity, that fluoridation is socially progressive. In other words, fluoridation is assumed to be socially rational, namely the best use of society’s resources to achieve a desirable end.

The trouble is that science by itself is quite inadequate to prove that fluoridation is socially rational. Additional assumptions are required, for example, that ensuring benefits of reduced tooth decay to the entire population takes priority over any violations of individual rights to avoid fluoridated water. But, in the social studies of fluoridation, such assumptions are never spelled out nor argued for. This
would undermine the rationale for trying to explain only the opposition to fluoridation.

These explanations of opposition to fluoridation implicitly ground their social analysis in a particular and inevitably limited view of the social world. This is not necessarily a shortcoming. The problem is that their assumptions about the social world are never made explicitly, and that, furthermore, these social assumptions are usually hidden behind the premise of a purely scientific foundation for fluoridation.

It is appropriate to note that many of the social scientists studying the controversy have seen it as their task to help promote fluoridation. Mausner and Mausner sought to understand the “disease” of anti-intellectualism and develop methods for combating it. Kegeles, in surveying social research on fluoridation, had some hope that “help for the [profluoridation] practitioner will be one of the eventual by-products.” Gamson, on the basis of his social psychological studies, offered recommendations for fluoridation proponents on what not to do in referendum campaigns. It is not surprising, then, that there has been a one-sided focus on opponents and a neglect of the social analysis of the promotion of fluoridation. In a review of social studies of fluoridation, Motz pointed out that there is an implicit profluoridation bias, and, hence, some possible research projects have never been undertaken, such as surveys of communities that have never been embroiled in fluoridation controversies.

A second theoretical problem with the usual explanations that focus on the reasons for opposition to fluoridation is that they make social analysis dependent on the current state of scientific knowledge. What if, in the future, scientists were to decide that fluoridation was wrong after all? Then, all the social analyses would have to be redone to explain the newly irrational support for fluoridation.

This is not just a hypothetical objection. There are many cases in the history of science in which the dominant viewpoint has been rejected and sometimes reinstated. Any method of social analysis that looks only to explain the irrationality of opponents of the dominant view would look foolish.

The theory of continental drift, for example, was once the dominant view. Then, it lost favor, and has since become the established view of today. Using social analysis to explain only opposition to continental drift, then to explain only support for it, and finally again to explain only opposition to it, would be a frustrating exercise.

In the case of fluoridation, where the dominant view differs in different countries, this would mean a social explanation for opposition to fluoridation in the United States and a social explanation for support of fluoridation in, for example, India. Indian sociologists have not written much on fluoridation — and certainly not in American social-science journals — so this theoretical dilemma has not been highlighted. One reason is that, in India, fluoride in water has long been seen as a health hazard and fluoridation has not been on the agenda. So, as a social problem, fluoridation has not been of special interest to social scientists there.

The limitations of the standard social science research on fluoridation can be traced to a general assumption that science is done in its own special realm, independent of the exercise of power, and that objective scientific knowledge enters into the social arena in some way or other. This means that power struggles over what counts as valid scientific knowledge are not included in the analysis. Certainly, that applies to the studies of demographics, alienation, and confusion. The idea of confusion, for example, implicitly assumes that there is a scientific realm in which clearheaded truth, rather than confusion, holds sway. This same assumption of a separation between scientific knowledge and social dynamics is also made in other types of studies of fluoridation.

The Group Politics Approach

This type of analysis essentially looks at the dynamics of interest groups in the social struggle over fluoridation. Typically, this means looking at dentists and other groups
promoting fluoridation, groups organizing opposition, government agencies, and the like. Studies in the group politics mold fall into the category of pluralist political science. They focus on tactics, alliances, policies, and outcomes. These studies often avoid the one-sided emphasis on demographic or psychological reasons for opposition, since both proponent and opponent groups are studied.

This type of analysis is useful at its own level, but it usually leaves out any consideration of social struggles over the status of claims about scientific knowledge. In other words, it makes the same assumption that science is carried out in its own separate realm, and becomes subject to social processes only when introduced into the public debate.

Combining the group politics approach with one or more of the other approaches would appear to offer greater explanatory power. But the result is still limited by the common assumptions made, such as the neglect of struggles over scientific knowledge and the neglect of struggles outside the United States.

Structural Analysis

Another method of analysis is to use concepts of social structure such as profession, class, capitalism, patriarchy, and the state. The idea of a social structure is a way to capture conceptually sets of human interactions that are regular and, in some way, patterned. For example, capitalism can be defined as a set of interactions associated with the ownership of the means of production and with the production and sale of labor power and goods in a market.

Focusing on structures does not mean that the role of individuals must be overlooked. Structures, after all, only come about when individuals behave in regular ways, as when entrepreneurs buy and sell goods in a market situation. In other words, structures are socially constructed. Structures are simply a convenient way of talking about certain recurring patterns of interaction.

Indeed, it can be misleading to think of the behavior of individuals as independent of these regularities. Individuals are caught in the structured expectations and behaviors of many others.

For example, a person might think it quite reasonable to move into an empty building. But capitalism is built on the ownership of property, which means that most people do not expect to be able to make use of vacant land or buildings and police can be induced to take action against those who do. Capitalism, thus, depends on people’s support for — or acquiescence to — property ownership, with the use of state coercion as an ultimate sanction. But these patterns of behavior are not forced on people. It is possible to challenge behavior associated with property ownership, for example, to undermine the loyalty of police and courts to certain owners. This is precisely what many squatters try to do.

Just as it is misleading to think of individuals as free agents — since they are constrained by other people’s regular patterns of action — so it is misleading to think of structures as independent of people’s activities, since it is always possible for regular patterns of activities to be challenged and changed.

Concepts of social structure can be used to examine scientific controversies, for example, by looking at the influence of professions, corporations, and the state in shaping agendas and pursuing certain goals. This approach has been almost entirely absent from analyses of fluoridation.

As I indicated in chapter 6, it is much easier to apply this sort of analysis to the promotion of fluoridation, whereas most analysts have looked only at the opposition. Furthermore, structural approaches are more commonly used by Marxian analysts, most of whom seem to have accepted the stereotype of antifluoridationists as right-wing individualists, and, hence, not found the fluoridation issue as one worthy of study. Structural analysis also has the same limitation as pluralist political analysis in that it does not delve into the struggles over scientific knowledge.

Although most social analyses of fluoridation focus on the opponents — assuming that scientific knowledge backs the proponents — there is a minority position that reverses the assumption. A few critics of fluoridation have
analyzed the dynamics of the controversy, focusing especially on methods of promotion, interest groups, and the like. This analysis is more likely to use the group politics approach. But it is in agreement with the rest of the research in the basic assumption that science is essentially separate from the social conflict. The difference is that the critics assume that the science supports the antifluoridation position, or at least does not support only the profluoridation stance.\textsuperscript{22}

From this brief survey of the main types of social analysis of the fluoridation controversy,\textsuperscript{23} it is easier to see where my own analysis differs. I have looked at both the promotion of and opposition to fluoridation, rather than just the opposition. The demographic, alienation, and confusion approaches are not sufficient for understanding the controversy. My main attention is on the struggles over the status of scientific claims about fluoridation. Rather than assume that scientific knowledge is in a separate category and exempt from social analysis, I have begun from the assumption that struggles over scientific knowledge should be analyzed in the same general way as other types of struggles.

**Sociology of Scientific Knowledge**

My approach grows out of a different tradition — the sociology of scientific knowledge. In this extension of the classical sociology of knowledge, all of science is opened for social examination. The processes by which scientists decide that certain claims deserve to be treated as facts are examined, just as the beliefs about religion, gender, or politics are examined.\textsuperscript{24}

The “strong program in the sociology of scientific knowledge”\textsuperscript{25} is based on four postulates.

1. All knowledge should be explained as resulting from social causes, called causality;
2. The investigation should be impartial with respect to the truth or falsity of the beliefs analyzed, called impartiality;
3. The same conceptual tools should be used to explain both true and false beliefs, called symmetry; and
4. The analysis should be able to be applied to itself, called reflexivity.

The strong program certainly provides a different entry point to the fluoridation controversy. First, social analysis is applied to claims about scientific knowledge as well as reasons for public opposition, emergence of interest groups, and so forth. Second, scientific claims both for and against fluoridation are analyzed using the same conceptual tools.

One of the most useful concepts is that of “resource” or “tool.”\textsuperscript{26} A resource is anything that is used by an “actor,” meaning, in this instance, someone or some group involved in the controversy. Resources include scientific knowledge, scientific publications, scientific status, and so on. Scientists can try to persuade each other of their views by using data, argumentation, personal prestige, charisma, publications, and many other resources.

One way to interpret this book is to say that, in each successive chapter, I have looked at the use of resources from a slightly different and ever widening point of view.

Chapter 2 deals with the scientific arguments. Scientific data and arguments are resources by which partisans try to convince each other and the public.

Chapter 3 deals with the coherency of viewpoints of partisans. In a sense, the different arguments in the debate are made coherent by the debate itself, and are, thus, made into a congealed, less vulnerable resource for waging further debate.

Chapter 4 deals with the credibility of partisans who are scientists, as credibility is both a resource and a target for attack.

Chapter 5 deals with professional attack. Professional power is a resource.

Chapter 6 deals with corporate power, which is certainly a resource and may have had some impact on the debate.

Finally, chapter 7 deals with methods of decision making, which themselves can be interpreted as resources.
Another valuable concept in analyzing the fluoridation controversy is “interest.” In chapter 2, the interests at stake are those of scientists in having a scientifically solid argument. Chapter 3 deals with coherency of viewpoints and could be said to treat the interests of partisans having viewpoints that stand up in public debate. Interests in scientific and public credibility are the core of chapter 4. Chapter 5 deals with the interests of the dental profession, and chapter 6 with the interests of certain corporations.

Long before chapter 7, however, I have gone beyond the usual ambit of the strong program, if not parted company with it. This is most obvious in the use of professional power and capitalism as tools of analysis. These are categories of social structure, as described earlier. They arise from different theoretical traditions that have seldom been meshed with the sociology of scientific knowledge. This is because the strong program has usually been applied to disputes carried out almost entirely inside the scientific community, such as over the existence of gravity waves or continental drift.

In such disputes, one can look at the shaping of claims of knowledge by general beliefs about society, by the career interests of groups of scientists, and so forth. But, whereas in such disputes there is some, usually tenuous, influence by wider social interests on the course of the scientific controversy, there is usually relatively little converse impact of the scientific controversy on society.

The fluoridation controversy is quite different. Not only are scientific, ethical, and political arguments mixed together in a vociferous debate but the credibility of scientists has been a subject of intense interest, with strong attacks mounted.

RELATIVISM

The usual theory of knowledge underlying the study of science is that scientific knowledge is an expression of truths rooted in nature, or at least as good an approximation as currently possible to such truths. This positivist approach is the basis of the assumption that controversies can be studied by examining the truth of scientific statements separately from the social dynamics. The strong program, by contrast, is built on a relativist picture of knowledge, which denies that there is any inherently superior way to determine truth rooted in nature. Science is, then, analyzed just as is any other belief system.

Note that in applying the strong program to controversies, only a “methodological relativism” is required. The analyst proceeds as if there were no privileged access to the truth. This is a procedure for social analysis, not a statement about reality or personal beliefs.

A common criticism of relativism is that it means that all beliefs are treated as equally true and that the social researcher — in this case, me — has abdicated responsibility for evaluating the scientific evidence. Both of these accusations are grounded in positivist assumptions. In other words, relativism is attacked on the grounds that it is not positivist. The arguments between positivists and relativists have been traversed at length elsewhere. Instead, let me simply outline how my analysis of the politics of knowledge about fluoridation does carry out a nonpositivist evaluation of scientific knowledge.

In looking at the struggles between pro-fluoridation and antifluoridation scientists, I have not sought to determine the “scientific truth,” but I have, instead, looked at the strategies used by different partisans. These strategies include presentation of data, theoretical argument, arguments including both technical and social dimensions in a coherent package, assertion of authority, attacks on the credibility of others, and so forth. The elements of these strategies include what is traditionally called scientific (data and theoretical arguments) and what is traditionally called social (authority and attacks), as well as mixtures (coherent arguments).

In my analysis, I have selected arguments, individuals, and cases that I consider to have been important in the controversy. This means that I have made an evaluation of their scientific and social importance.

For example, I have given considerable attention to arguments about the benefits of
fluoridation. My assessment is that these arguments are important because the science in the area has been persuasive. The proponents have used arguments about benefits — and evidence to back these arguments — as the foundation of the promotion of fluoridation. The opponents have used arguments and evidence critical of claims about benefits as effective tools to challenge fluoridation.

On the other hand, I have given little attention to attacks on fluoridation on the grounds that sodium fluoride is used as rat poison. While this argument is regularly brought up by lay opponents — and sometimes in a rhetorical fashion by scientist opponents — it has played a subsidiary role in the controversy, so far as the use of scientific claims is concerned.

Note that my selection of arguments does not require an assessment of scientific truth rooted in nature, as assessed by authoritative experiments and the like. Rather, I examine the scientific claims in the social context of the debate. But I have not treated all claims as equal. Not all are worthy of the same attention.

Rather, I concentrate on claims that are the most potent or persuasive in practice. This can be because they are, in positivist terms, either scientifically convincing or politically convenient. In practice, from the relativist’s perspective, these two categories of science and politics are not separated.

In my analysis, I have certainly made judgments about the quality of evidence, argument, and intervention. I have concentrated on opponents of fluoridation who are scientists, such as John Colquhoun, Mark Diesendorf, Philip Sutton, George Waldbott, and John Yiamouyiannis, because their contributions have been perceived as sufficiently influential to mobilize supporters and disconcert proponents. I have given less attention to scientists on the fringes of the debate, either because their scientific merit has less credibility even with knowledgeable opponents or because, whereas their science is respectable, their work has not been brought center-stage in the controversy.

A similar selection and evaluation process applies to my discussion of proponent arguments. I have cited works of individuals such as Brian A. Burt, Frank J. McClure, John J. Murray, and Andrew J. Rugg-Gunn because their contributions to the debate, both scientific and social, have been treated with great seriousness.

What I have not done is attempt an assessment of the scientific evidence for and against fluoridation as if that evidence is separate from the social evaluation of the controversy. Indeed, my analysis is designed to show why such an assessment, if presented as separate from social considerations, can be misleading.

Knowledge about fluoride is not separate from society but has been generated in a context in which therapeutic use and, since the early 1940s, policy decisions have been key considerations. The context of much fluoride research has been highly charged and often polarized into profluoridation and antifluoridation molds. “Nonscientific” ethical and political considerations are crucial, and have been tightly linked to scientific claims throughout the debate.

Even more dramatically, the attacks on the credibility and activities of scientists among the leading opponents have been important in the assessment of the scientific status of both profluoridation and antifluoridation claims. The attacks have also undoubtedly been important — although in ways which can only be guessed at — in shaping both research into fluoride’s effects and research into alternatives to fluoridation.

Relativism liberates the social scientist from the constraints of acquiescing to the current scientific orthodoxy. The social analysis can range more deeply into scientific areas. That, of course, may offend powerful scientists and their allies, and perhaps this is one reason why relativism is applied to current controversies less often than it might be.

From the point of view of the strong program, there is no such thing as a neutral, unbiased assessment of scientific evidence. Rather, those assessments that are more persuasive, and that seem to others to be more objective, are the assessments which are sensitive to the diverse facets of the social context in which the science is embedded. It is a compliment rather than a criticism to say that
Edward Groth III, in his writings on fluoridation and including his commentary in this book, accomplishes such a persuasive assessment precisely because of his awareness of the social influences on fluoride research. He is willing to consider scientific evidence damaging to fluoridation in spite of its rejection by proponents because he is aware of the processes used to destroy the credibility of critics.

But he is also willing to be critical of evidence often raised by antifluoridationists. He is aware of the polarized nature of the dispute and uses this awareness to assist him in avoiding the assumption, encouraged by partisans on both sides, that, if evidence doesn’t support one side, it must support the other. A positivist might say that Groth is surveying the scientific evidence. A relativist might say that he is presenting a persuasive account of the scientific evidence, informed by his assessment of the social context.

THE ROLE OF THE RESEARCHER

For all their differences, the positivist and relativist approaches have a surprising convergence when it comes to studying contemporary controversies. Each of them assumes that the researcher is a separate, neutral observer. This is obvious enough when it is assumed that objective knowledge is to be sought about science and society. Being a partisan on the issues would certainly seem to make objectivity difficult if not impossible. As a result, it is usually assumed without discussion that analysts are not and should not be involved in the controversy themselves. If they are, then bias is assumed.

More intriguingly, relativist approaches lead to the same result. The strong program in the sociology of scientific knowledge is actually based on the traditional scientific method. Causal explanations are sought, and the same explanatory mechanisms are used to analyze all social beliefs, including scientific knowledge. Ironically, in this respect, relativism is more like the traditional positivist model of science than is positivism in the social sciences. There is no suggestion that the researcher can or should be involved in the controversy.

The strong program’s requirement of reflexivity — that the theory should apply to itself — would seem to allow for researcher participation. But in practice reflexivity is taken to mean that methods of explaining beliefs should also be able to be applied to the beliefs of the analyst. The social explanation of the rise of social theory is one thing; involvement in the controversy being studied is another. In practice, relativist analysts of controversies have almost exclusively studied either historical cases, which allow a nice separation of the researcher and the researched, or contemporary cases that are restricted to fairly narrow disciplinary communities. In the latter case, the analyst’s involvement does little to disturb the controversy itself, especially when the products of social research are esoteric articles in specialist social science journals.

Separation of the researcher and the researched may work in some cases, but practical experiences show that it often cannot be sustained in dealing with contemporary controversies with a strong public involvement. To some extent, the social researcher is inevitably involved in the controversy being studied.

I have already described the commitment to fluoridation by many social scientists who have studied the controversy. In some cases, the social scientists were “recruited” by profluoridationists to study the issue. For example, the initial incentive and funding for the major study by Robert Crain, Elihu Katz, and Donald Rosenthal was provided by the United States Public Health Service (USPHS). These researchers were obviously sympathetic to fluoridation.

It is not surprising that such studies are quite useful to proponents and have often been cited by them. For example, J. M. Dunning, in a textbook on dental health, states that social scientists are the allies of profluoridationists. The social scientists sometimes become involved in overt partisan activity. Historian Donald R. McNeil, author of the classic history The Fight for Fluoridation, has
repeatedly taken a strong profluoridation stand.\textsuperscript{32}

This sort of involvement by earlier social scientists in the fluoridation issue was not seen as a problem, nor as a violation of objectivity. This is because they accepted a positivist picture of science, accepted the claims of dental authorities about fluoridation, and believed that fluoridation was socially progressive. Therefore, partisan involvement meant being a partisan on behalf of truth, which was treated as unproblematic.

Just as there is a strong connection between assuming that fluoridation is scientifically proven and undertaking a social analysis of reasons for opposition, so there is a strong connection between opposing fluoridation and undertaking a social analysis of the promotion of fluoridation.

Opponents can use structural analysis to explain the promotion of fluoridation in terms of other than rationality. Explaining also becomes “explaining away.” Strictly in terms of logic, explaining the promotion of fluoridation by its compatibility with the interests of powerful groups does not mean that fluoridation is any less desirable. But, in practical political terms, structural explanations are threatening to those policies that are “explained.” Structural analysis is a challenge to any claim of pure rationality.

Aside from the crude statements by opponents that fluoridation is a plot by big business and big government, few studies have developed even a moderately careful analysis of the promotion of fluoridation. In each case, the analysis has been linked to opposition to fluoridation.

An early important study was by Michael Wollan, who wrote an article entitled “Controlling the Potential Hazards of Government-sponsored Technology” which was published in 1968 in the George Washington Law Review.\textsuperscript{33} The article examined how technology assessment was being performed in the United States, and analyzed three case studies: weather modification, engine noise from supersonic transport aircraft, and fluoridation. In discussing fluoridation, Wollan focused on the vested interest of the USPHS in a measure it had endorsed, making impossible a proper continuing assessment of the measure.

Opponents have frequently cited Wollan’s article and distributed copies of it. Wollan was not involved in the opposition to fluoridation before this article, but, after it appeared, he opposed fluoridation on a few occasions before his early death in an automobile accident.

Another important study was done by George L. Waldbott, Albert W. Burgstahler, and H. Lewis McKinney, and included as part of their 1978 book Fluoridation: The Great Dilemma.\textsuperscript{34} The primary author of this book was Waldbott, and, indeed, it is written in the first person singular. Waldbott was the leading opponent of fluoridation in the United States for some twenty years, beginning in the mid 1950s. Burgstahler, professor of chemistry at the University of Kansas, has also been an active scientist opposing fluoridation. McKinney is a professor of history of science at the University of Kansas. The structural analysis in Fluoridation: The Great Dilemma thus forms a part of their overall case against fluoridation.

Wendy Varney’s book Fluoride in Australia: A Case to Answer, published in 1986, is the most important recent structural analysis of fluoridation.\textsuperscript{35} Varney’s treatment is the most careful and comprehensive yet available, drawing on theoretical accounts of capitalism and the professions as well as a large amount of data about fluoridation in Australia and elsewhere. Varney’s book is based on a thesis done in the Department of Government at the University of Sydney. Before doing this study, Varney had been an environmental activist but had played no role in the fluoridation issue. But after writing the book, she took a public stand against fluoridation on a number of occasions, both in talks and interviews.

Mark Diesendorf, a leading opponent in Australia, collaborated with Varney in writing an article on “Fluoridation: Politics and Strategies,” published in 1986 in the Australian journal Social Alternatives.\textsuperscript{36} This article develops an analysis along the lines of
Varney’s analysis and draws conclusions about how to oppose fluoridation. John Colquhoun, a former dental public health officer who switched sides to become a leading opponent of fluoridation in the 1980s, later wrote his doctoral thesis at the University of Auckland on the topic of education and fluoridation, including a structural analysis of the promotion of fluoridation.\(^{37}\)

These examples show the strong link between making a structural analysis of the promotion of fluoridation and opposing the measure. Waldbott, Burgstahler, Diesendorf, and Colquhoun were active opponents of fluoridation who were scientists and who later wrote about the role of corporations and the dental profession in promoting it. Wollan and Varney, as social scientists, apparently did their analyses along these lines first, and then were drawn into the debate on the opposition side.

What these examples show is that the type of analysis which a person makes of the polarized fluoridation controversy is influenced both by his or her stand on the issue and, in turn, influences his or her further participation in the argument. Any hope of a value-free analysis, or a value-free mode of analysis, appears to be misplaced. Those who want to maintain the misleading appearance of value-free social-science research are best advised to avoid studying contemporary controversies, or, as an alternative, to publish only abstruse articles in obscure specialist journals so that partisans are not tempted to use the research for their own ends.

This is not my aim in writing this book. Rather than attempting to keep myself separate from the debate, my involvement may actually lead to deeper insights than are otherwise possible. My own experiences serve to illustrate this.

My initial study of fluoridation was made possible without much personal interaction with the controversy, simply by obtaining and studying various documents that are readily available to the public. But this changed when I undertook interviews with leading Australian partisans who are scientists, as described in chapter 3. Only a few of the opponents and proponents knew me, or had even heard of me, before I interviewed them. But a viewpoint was formed in some cases.

Halfway through my long interview with fluoridation proponent Elsdon Storey at the University of Melbourne, he told me that he knew what I was going to say in my research, because he had seen a copy of a paper I had presented describing cases of suppression of dissent in several fields, including fluoridation.\(^{38}\) Storey informed me that he did not wish to be quoted in my paper unless he was given a complete draft to okay before anyone else saw it.

After returning from my interviews in Melbourne, I received a letter from Jack Martin, another Melbourne proponent whom I had interviewed before meeting with Storey. Martin also requested inspection of the full manuscript before it was seen by anyone else. He added that he was surprised that my university was funding such an “unscientific” study.

What I did in response to these requests was to remove from my draft paper any direct reference by name to views expressed in the interviews with these two individuals.\(^{39}\) I then sent the draft paper (the essence of which is chapter 3 in this book) to all 17 proponents and opponents I had interviewed, inviting their comments. Five of the six opponents furnished comments, some of which were quite critical. By contrast, not a single proponent provided comments. The only replies were from Storey, who criticized my standard of work and said he did not want to be associated with my article in any way; and Martin, who said the article was trivial and biased and requested that his name be omitted.

The obvious explanation of the different responses to my paper lies in the symmetrical approach that I had adopted. I described the coherency of viewpoints of both proponents and opponents, and I presented the arguments on both sides. Because proponents generally maintain that there is no credible scientific opposition to fluoridation, my analysis appeared to give the opponents far too much credibility.
A similar one-sidedness prevailed when I tried to obtain comments on the first draft of this book from scientifically knowledgeable proponents and opponents of fluoridation. I had no difficulty in obtaining significant comments from the only three opponents I approached: Albert Burgstahler, John Colquhoun, and Mark Diesendorf. This was not surprising, as each had readily corresponded with me earlier. Obtaining comments from proponents was more difficult. In the end, I wrote to twelve leading proponents in several countries before obtaining comments from Brian Burt, Michael Lennon, John Small, and Donald Taves. Had I not received their comments, it would have been more difficult to obtain a good picture of the proponents’ case, and easier to have been drawn into the opposition camp.

My point is that, as soon as one begins interacting with partisans in a polarized controversy, there is no neutral position. If I had adopted a strong profluoridation position, dismissing critics as not to be taken seriously, then it would have been difficult, to say the least, to maintain communication with the critics. On the other hand, taking a symmetrical position meant alienating many of the proponents. Even my symmetrical position—which apparently led the Australian proponents to cease communications—has led to criticisms from some antifluoridationists who believe I have given too much ground to the proponents.20 The pressures for becoming an overt partisan—or avoiding the controversy altogether—are considerable.41

One possible way around this problem would be to delay publication and the revelation of one’s perspective until all research is completed. Unfortunately, this strategy does not allow for a crucial part of social research: that is, the development of the researcher’s credibility with particular audiences. By publishing, one’s authority can be boosted in the eyes of some participants in the controversy, and this can lead to acquiring materials and insights not otherwise obtainable.

This was apparent in my correspondence with numerous individuals involved with fluoride around the world. Before I had written anything about fluoridation, I received helpful replies from some to whom I wrote. But, after writing drafts of papers and, even better, having had papers published, my status as a person to be reckoned with was increased. From several individuals, I received valuable personal information and documents that I am sure would not be sent to the casual inquirer. This sort of response was more likely to come from opponents of fluoridation or from those not necessarily against fluoridation, but who had run afoul of the proponents. But I also received some very valuable materials from proponents. On the other hand, many proponents—and some opponents—did not supply material that they might have shared.

There is nothing exceptional about this sort of response. Most people are more likely to spend time and effort and to reveal information to those whom they believe are likely to treat it responsibly and to have an impact. Sending prior publications is an excellent way of showing the sort of results one is likely to produce in the future.

Another consequence of writing about fluoridation was that my articles were taken up by partisans for their own purposes. Several opponents have told me that they have circulated copies of my papers to others, and the papers have also been cited on occasion by opponents. I am less sure of how proponents have treated the papers. In any case, the point is that a researcher, intentionally or otherwise, can be incorporated into the controversy by partisans. In my case, the involvement has been mainly via my publications. Ironically, my status as a social scientist entirely separate from the controversy allows my work to be used more effectively by partisans.

Partisan involvement is a more difficult issue for relativists than positivists, although it is not necessarily more compromising. As already indicated, a relativist analysis of claims to knowledge normally must be supplemented by an analysis of power relations. Part of this latter analysis can involve an examination of the ways in which partisans are able to mobilize or neutralize others, including social scientists. In other words, the analysis can be applied to itself.
The researcher who is studying scientific controversies makes value judgments in a number of ways, including many detailed points such as which bits of evidence to emphasize, which partisans to give credence to, which arguments or power plays to discuss, and so forth. But, prior to these detailed judgments, come some wider choices.

What issue should be studied? Dealing with a historical case usually allows the analyst to escape scrutiny by partisans. Dealing with a bitterly contested issue with public dimensions makes it more difficult to appear to be neutral.

What is the audience of the research? Writing recondite social-science jargon for specialist journals means that partisans will take less notice. It also means that social scientists have abjured making a contribution to the debate.

What conceptual tools are used in the analysis? Positivism is generally useful for supporting the side with strongest claims to scientific backing. Relativism is generally more useful for supporting the side with less scientific credibility. But it remains possible to try to adapt any particular analysis to counter these tendencies.

Finally, to what degree is the analyst involved in the controversy? Research built on assessment of documents without interaction with partisans, and publication in esoteric specialized journals, allows low involvement at the expense of the understanding to be gained through direct contacts, inside channels of information, and participant observation.

My position is that there is no best way to study the fluoridation controversy. A “best way” assumes agreement on the aims of the social analysis, and that agreement does not exist.

Many analysts have supported fluoridation and, consciously or unconsciously, used their analysis to support the cause of fluoridation. For this purpose, a positivist framework and relatively accessible publications are most suitable. The same applies to the very few analysts who have opposed fluoridation.

Many analysts, it is safe to say, use studies of the fluoridation controversy primarily as a means to “contribute to social science,” as well as enhance their own reputations and promote their careers. For this purpose, a more independent stance toward partisans and an orientation toward specialist publications is dictated. A low-key, tacit support for fluoridation may also help, since most editors and referees for relevant journals have also automatically supported fluoridation.

But the intellectual marketplace is competitive, so some researchers may find it to their advantage to stake out new conceptual territory, tying their prestige and careers to unconventional ways of doing things. They will, naturally, justify their approaches in terms of contributing to a deeper understanding of the social world — just as did those following the prior orthodoxy. This is one way to put in perspective the development of the strong program in the sociology of scientific knowledge. This approach provides new insights, presents new dilemmas and, most importantly for social researchers, opens up new areas for analysis.

That is what I have tried to do in this book. I wanted to show how the science in the fluoridation controversy can be studied in its social context. Personally, I am not particularly concerned about supporting or opposing fluoridation. My interest lies in the exercise of power within science and the implications of this for democratic decision making. I believe the method of analysis I have chosen helps in dealing with these issues.

But my own intentions are only part of the story. Having analyzed the fluoridation controversy, my own work becomes a part of it. Others will now make their own decisions about how to use it.
NOTES


11. Mausner and Mausner, op. cit.


18. This is explicit in the mammoth volume edited by Engelhardt and Caplan, op. cit., for example at p. 5: “A scientific controversy with a heavy political and ethical overlay is not, then, one controversy but a scientific controversy (or controversies) plus a controversy (or controversies) concerning social and political theories and viewpoints.”


20. The major example is Wendy Varney, Fluoride in Australia: A Case to Answer, Sydney: Hale and Iremonger (1986).

21. The only left-wing analysis of fluoridation of which I am aware, prior to Varney’s, is by M. Klerer in “The Fluoridation Experiment,” Contemporary Issues, vol. 7 (1956): 119-167. Incidentally, I have never seen a citation to this paper. I thank Allen Hunter for drawing it to my attention.


23. The work of Allan Mazur deserves separate mention here. In “Disputes Between Experts,” Minerva, vol. 11, no. 2 (April 1973): 243-262, later incorporated in The Dynamics of Technical Controversy, Washington, D.C.: Communications Press (1981), he analyzes the rhetoric over scientific knowledge on both sides of the controversies over fluoridation and low-level ionizing radiation, but only hints at more than rhetorical confrontation. Underlying Mazur’s apparently symmetrical analysis is a positivist conception of scientific knowledge, which he clarified for me in correspondence. In a later study, “Opposition to Technological Innovation,” Minerva, vol. 13, no. 1 (spring 1975): 58-81, Mazur focuses on the opponents. (For the limitations of his model of media influence, see Jasper, op. cit.) To my knowledge, he has never carried out a study of the promotion of fluoridation, possibly reflecting a post-1973 assessment of the weakness of the scientific case against fluoridation.


There is also a considerable literature on resources used in social struggles, for example by social movements. *See* for example J. Craig Jenkins, “Resource Mobilization Theory and the Study of Social Movements,” *Annual Review of Sociology*, vol. 9 (1983): 527-553.

I do not discuss this literature further since my focus is on struggles over scientific knowledge. Note that applying resource mobilization theory to the fluoridation controversy would mean focusing on the opponents. A more symmetrical approach would examine both the proponents and the opponents as contending movements, with differential access to resources associated with the state, corporations, professions, and other areas of society.


29. I am indebted in this section to discussions with Evelleen Richards and Pam Scott that are part of our ongoing collaboration on the role of the researcher in contemporary controversies.

30. Crain et al., op. cit., v and vii.


33. Wollan, op. cit.

34. Waldbott et al., op. cit.

35. Varney, op. cit.


39. I did mention Storey’s views as presented in a letter to a newspaper.

40. I have received significant criticisms from, among others, P. C. Blount, Albert Burgstahler, Robert Mick, and John Yiamouyiannis.

41. Edward Groth III, one of the few to attempt to avoid taking sides, commented on his difficulties in a letter to me dated 22 September 1988: “… my work became known to the anti-fluoridationists very early on (since I had contacted them for a lot of my research materials). They immediately did try to use me and my ideas to advance their own goals, and that led to a series of attacks on me, some rather vicious, from the pro-fluoridation forces. There was indeed enormous pressure to choose a side, or withdraw. I didn’t, because I never saw myself as interested in the outcome of fluoridation decisions. I was interested in the process, and I was convinced that society needed to find better ways to deal with this issue. I managed to maintain the integrity of that posture pretty well, to my own satisfaction. But the proponents still regarded me as an ‘anti,’ because as we both know, neutral or symmetrical critical approaches help the antis by legitimizing the controversy. Efforts were made, therefore, to discredit me personally and to portray my dissertation as an antifluoridation tract.” For Groth, the intimidating climate from the proponents was a fairly small negative factor, but it was still sufficient to keep him from publishing further in the field, given that his position did not require publication for career purposes.
The fluoridation controversy: which side is science on?
A Commentary by Edward Groth III

(EDITOR’S NOTE: Edward Groth III is a biologist who has specialized in the study of policy decision-making processes on environmental and public health issues. He holds an A.B. degree in biology from Princeton University, and a Ph.D. in biological sciences from Stanford University. His doctoral dissertation concerned a study of two issues of science and public policy — air pollution control and the fluoridation controversy. He worked for five years on the staff of the Environmental Studies Board of the National Research Council in Washington, D.C., preparing reports on environmental problems for the federal Environmental Protection Agency and other government agencies. Since 1979, he has been on the staff of Consumers Union, the publisher of Consumer Reports magazine, where he is currently associate technical director for Policy and Public Service. The views expressed here are his own, and do not represent positions of Consumers Union or any other organization.)

INTRODUCTION

In this book, Brian Martin has produced the most penetrating and authoritative analysis of the fluoridation controversy yet to emerge from the multidisciplinary social studies of science. (And, from my perspective, it’s high time someone did!)

Nevertheless, Martin’s assessment leaves me unsatisfied. I want it to say more about two key questions.

First, he takes the existence of the controversy as a given. Then, he examines the arguments and behavior of the advocates on each side. But why does controversy persist over fluoridation, after fifty years of debate? Is this, as the proponents often insist, a “fake” controversy, without real merit, and spurred by unscientific “antis”? Or is the idea of fluoridation intrinsically controversial?

Second, the fluoridation debate is dominated by disputes over scientific issues. While Martin recounts what both sides say on many of these questions, he makes no attempt to assess the quantity or quality of evidence for the arguments of each side. Who is right? Are they both wrong? We need to know.

Evaluating such a massive, complex body of data is a daunting task, even for an author steeped in the environmental health sciences. But to omit doing so is like leaving yeast out of bread dough; the end product is flat and unsatisfying without that vital ingredient.

In this essay, I will attempt to fill those two voids. I will demonstrate — rather decisively I believe — that the controversy over fluoridation is, indeed, inherent in the proposal and absolutely unavoidable. On the second task, I will venture into somewhat riskier territory. A detailed review of the literature is neither appropriate for the expected audience of this book, nor is it feasible in the available space. I plan, instead, to present my own admittedly subjective impressions of the evidence, based on several thousand papers that I have read over twenty years. My statements will necessarily be very general. For readers who prefer not to accept my characterization of the evidence, I will supply references to more detailed scientific reviews as reasonable starting points for independent examination of the literature.

A GENUINE CONTROVERSY

Proponents of fluoridation often assert that there really is no legitimate debate. Political controversy persists, the argument goes, only because misinformed, antiscientific opponents refuse to accept the overwhelming scientific evidence of fluoridation’s effectiveness and safety. As one often-cited American propagandist has stated, “The survival of this fake controversy … repre-
sents one of the major triumphs of quackery over science in our generation” (Consumer Reports 1978).

When “pros” take that posture, an analysis like Martin’s or my own (Groth 1973, 1980) that treats the controversy symmetrically — that is, looks critically at arguments and behavior of both the proponents and the opponents — legitimizes the opposition by implicitly treating the controversy as genuine. It is, thus, incumbent on us, I feel, to state explicitly why we believe that the controversy over fluoridation is legitimate.

A Clash of Values

The first key to the answer lies in looking closely at what the dispute is really about. A casual observer might think that the debate over fluoridation is a scientific dispute, but that’s not so. The controversy is really over a question of social policy: Shall the public water supply be used as a vehicle to treat the population with fluoride to help prevent tooth decay?

Assessments of risks, benefits, and economic effects of the measure are, to be sure, scientific tasks. But science cannot say what degree of risk is acceptable in exchange for expected benefits. Neither can science say whether it is morally acceptable to treat the public with a prophylactic agent through the water supply, or whether universal effortless treatment to prevent tooth decay should take precedence over a citizen’s right to decide what treatments — and what risks — he or she will accept.

These issues are pure value judgments. They require social choices among competing priorities. And people clearly disagree, often vehemently, over such value judgments. There is no single “right” answer to such policy questions. They demand political solutions, and, significantly, the political choice posed by fluoridation has no compromise outcome. A water supply is either fluoridated, or it isn’t. It is, therefore, not surprising that the debate over the measure is polarized into committed “pro” and “anti” camps.

A Clash of Risk/Benefit Perceptions

Social psychologists have recently documented how average citizens perceive risk/benefit issues quite differently than many experts do (Slovic 1987), which helps explain why experts often have trouble communicating with the public about risks.

Although a minority dissents, most experts on fluoridation see the benefits of the measure as solidly proven and large, and they view the risks as unproven, remote, and minuscule — if, indeed, any risks exist at all. From that viewpoint, fluoridation seems sensible and sound.

But the public sees things somewhat differently. To most average people, the benefits of fluoridation are invisible. Nobody “sees” cavities their children don’t get. Most people also do not regard tooth decay as an especially serious health problem.

When it comes to risks, experts tend to demand some concrete evidence of hazard. But consumers expect products and health treatments to be proven safe. They are more inclined than experts are to see sketchy evidence as grounds for concern about safety. The public in general is also risk-averse. Given a choice, they would prefer to accept zero additional risk, especially when lower-risk or no-risk alternatives are available.

While experts generally focus on the magnitude of a risk as its critical dimension, and judge risks below a certain size to be trivial and socially acceptable, average citizens seem much more attuned to the quality of the risk. Certain qualities also greatly magnify public reluctance to accept a risk. Natural hazards are much less frightening to most people than hazards that originate from technology or human actions, even if the latter are identical — as in artificially versus naturally fluoridated water — or objectively much smaller.
Voluntarily assumed risks — those in which the individual feels in control of his or her own fate — are tolerated much more readily than even negligible risks that are imposed on people without their choice or control. If the risk is perceived as morally unacceptable, involuntary risks may provoke outrage far out of proportion to the size of the risk. For instance, people may smoke cigarettes but object strenuously to minute pesticide residues in their foods (Sandman 1987).

The public’s point of view on these matters is no less “rational” than is that of the experts. The two views are just different. Such differences help explain why experts and average citizens often don’t see eye-to-eye on fluoridation.

A Clash of Moral Perceptions

Scientific questions about fluoridation hold out at least a hope of being answerable with objective evidence, but the moral dimensions of the debate are intensely and irremediably subjective. Here, too, the issue is polarized.

To health authorities, fluoridation advances social justice by providing dental caries prophylaxis to all children, including many of the poor who would not otherwise be able to afford proper dental care. In the eyes of pro-fluoridationists, it is morally wrong for a community not to provide that benefit.

To antifluoridationists, fluoridation is, in itself, morally wrong, because it violates individuals’ rights to determine what happens to their own bodies. Even those who see the value of fluoride treatment consider the administration of uncontrolled dosages through the water supply to be a violation of medical ethics. “Antis” reject “pro” comparisons with vaccination and chlorination, arguing that dental caries is neither life-threatening nor is it spread through the water supply. Thus, compulsory mass treatment to prevent dental caries is unjustified. Each side sees its own as the morally superior position, and attacks the other side’s posture in ethical terms, such as “denying poor children the benefits of fluoridation” or “forcing medication down our throats,” respectively.

Decisions by courts — which have ruled both for and against fluoridation in different cases — don’t resolve this dispute, as legality and morality are rightly perceived as separate issues.

A Clash of Experts

Disputes over value judgments in fluoridation decisions would persist even if the scientific evidence were complete and unequivocal, and all experts agreed on what it meant. But it is unreasonable to expect such unanimity of either science or scientists. The science on any debate over an environmental health issue shares these common features

Uncertainty. Research simply cannot answer all questions that “matter” on any environmental health topic. Even the best studies raise new questions while offering tentative answers to old ones. Available research tools are rarely potent enough to yield unqualified proof of cause and effect, especially when effects of environmental agents on human health are concerned. Critical knowledge gaps always remain.

Expert Judgments. Because of the irreducible uncertainties inherent in the science itself, policy decisions depend on extensive interpretation of the evidence by experts who must make many subjective judgments in the process.

What is a “good” study? How much evidence does it take to be “convincing” on a particular point? What are the implications of particular evidence for human health? When two different studies on a key issue reach conflicting conclusions, where does the truth lie?

Such questions have no unequivocal answers. Two equally qualified experts can study the same body of research and reach opposing scientific conclusions. Experts are human, and their own values and social views are often intermingled with their “scientific” advice.
For instance, an expert whose chief concern is dental caries prevention might look at inconclusive evidence of harm from fluoridation, and advise that there is no proof of adverse effects. So, fluoridation should proceed. An expert whose chief concern, however, is avoiding unnecessary risks might look at the same body of evidence and conclude that fluoridation should be held in abeyance until more definitive proof of safety is available. The experts might actually disagree less over the evidence than over the philosophical issue of where the burden of proof should lie in disputes over public health procedures.

Disagreement among experts is the norm in public-policy debates with scientific components. It is both commonplace and appropriate for policy makers and the public to hear conflicting scientific opinions. The common profluoridation claim that all “qualified” experts support the effectiveness and safety of the measure is simply not credible; science and scientists are never so unambiguous. The apparent unanimity on fluoridation has its origin in political processes as described in Martin’s analysis, not in the underlying science, as I will show later.

A Clash of Professional Perspectives

Two distinct professional fields — dental public health and environmental health — might lay claim to research on the possible effects of fluoridation. Each has its own unique perspective, and the two fields differ in basic goals, concepts, methods, and intrinsic biases, enhancing the likelihood of disagreements among experts on questions related to fluoridation.

Dental Public Health. Fluoridation research originated within this field nearly 60 years ago. The basic goal of this subdiscipline is the general promotion of oral health, including the prevention of tooth decay. Dental public health practitioners see fluoridation as a most valuable weapon in the war against dental caries. Their primary scientific goal has been to demonstrate that adding fluoride to unfluoridated water supplies has the same beneficial effects observed in naturally fluoridated communities. Secondarily, they have sought to demonstrate that neither natural nor artificial fluoridation poses unacceptable health hazards for people who drink the water for a lifetime. From the dental public health perspective, fluoride research should be used to support a major public health benefit.

Environmental Health. This second field of knowledge treats fluoride as it would any other toxic natural element. It seeks to assess exposure from all sources; to identify populations with excessive exposures or risk-enhancing personal characteristics; to identify potential biological effects of exposure and their underlying physiological mechanisms; to determine the dose-effect and dose-response relationships that link exposure and effects; to identify risk-enhancing or risk-reducing variables; to estimate the likelihood and magnitude of effects at any given level of exposure; and to assess safety margins between typical dose levels and those that may cause adverse effects. Experts trained in the environmental health perspective are concerned primarily with risks, and with protecting the public from possible harm. They use research primarily to support health and safety standards and pollution control regulations.

These two legitimate and well-established professional perspectives are, inherently, somewhat adversarial toward each other. While dental public health practitioners seek to use scientific data to promote benefits, environmental health practitioners try to use research to protect against potential health hazards. In public policy debates, these two legitimate points of view would normally clash, and policy makers would have to resolve conflicting interpretations and priorities.
But the fluoridation debate is not a normal policy-making context, and the two clashing perspectives generally have not received balanced attention in the dispute. The reasons for this are largely historical and political.

**A BRIEF HISTORY OF FLUORIDATION RESEARCH**

The scientific and political histories of fluoridation are inextricably intertwined. Once fluoridation became an explosively controversial political issue around 1950, the dispute had profound effects on the subsequent conduct of research and the interpretation of results.

Martin’s monograph recounts the familiar history of early fluoride research. Studies beginning in the 1930s correlated fluoride levels in community water supplies with resistance to dental caries. The idea that tooth decay could be largely prevented by adjusting the mineral content of water supplies proved irresistible to public health leaders, and “demonstration” projects with artificial fluoridation were begun in 1945.

While those studies were under way, enthusiastic advocates of fluoridation began an intensive lobbying campaign to attain widespread official approval for and endorsement of the measure. Those early “pros” believed that naturally fluoridated communities provided all the evidence needed that fluoridation was effective and safe. They campaigned tirelessly, and met with much political success. In 1950, the United States Public Health Service (USPHS) yielded to the pressure and, over the objections of its own scientific authorities who felt that an endorsement was premature, officially endorsed fluoridation. Proponents rapidly accumulated endorsements from professional societies and health organizations and felt that their battle had been won. They were wrong.

Early promotional efforts were met by strong opposition to fluoridation, for all the reasons described earlier. Many early opponents were scientists, who criticized the “pros” for failing to complete the demonstration studies before endorsing fluoridation, and who raised questions about possible toxic effects that had been inadequately investigated.

In truth, the USPHS had conducted very few studies to assess potential toxicity of fluoridated water at the one-part-per-million level. In the next fifteen years, numerous safety studies were done. But most were conducted by USPHS scientists who were openly defending a controversial policy from vigorous political attacks. These studies can therefore be criticized for obvious potential bias, as well as subjected to normal scientific criticism.

While this research proceeded the political battle raged, and the controversy rapidly polarized. Proponents of fluoridation learned that the public, aroused by allegations from the “antis” of harm from the measure, would not accept objective statements on questions of safety. Rather than say, “None of the evidence we have seen so far indicates a significant risk, but there are still unanswered questions,” the “pros” found that they had to be dogmatic: “Research has proven, beyond question or doubt, that fluoridation is absolutely, unequivocally safe for everyone.” To say less was to invite political defeat.

By the mid-1960s, research on potential adverse effects of fluoridation had essentially come to a halt within the USPHS. The emphasis had shifted to political promotion. Proponents felt the earlier studies were adequate to support their case, and that continuing research on questions which had supposedly been answered could prove to be politically awkward. Thus, for the past twenty-five years, there has been little or no official effort to search for possible side-effects of fluoridation, at least in the United States. The USPHS has pursued reactive research, seeking to counter claims or findings used by the antifluoridationists, but has not actively sought evidence of possible harm.

The seeds of the imbalance between the two scientific perspectives on fluoride research —
noted in the previous section — are evident in this history. Virtually all research supporting fluoridation was done by proponents of the dental public health (DPH) perspective, including USPHS scientists; those associated with the “demonstration” studies; and a few outside experts who were recruited to assist in promoting this novel public health measure. Although research on the potential adverse effects of fluoridated water might obviously fall within the environmental health (EH) perspective, in this case, the work was done almost exclusively by USPHS scientists and others in the DPH camp. The few scientists with EH credentials who participated in research on fluoridation were willing converts, most of whom also played important roles in political advocacy of the measure.

Historical accidents account for the dominance of the DPH perspective in fluoridation research. The same agency (the USPHS) was responsible both for promoting fluoridation and for assessing its safety. Today, such a conflict of interest would likely be recognized and dealt with. For example, in the United States, nuclear power is promoted by one agency, while its safety is regulated by another agency. But political institutions had not come to terms with this problem in the 1950s. Perhaps more significant was the lack, in the early years of fluoride research, of a well-defined discipline of environmental health. That field really came into its own in the 1960s and 1970s. Neither the concepts and methods now used routinely in environmental health research nor institutions that would foster such research (such as the U.S. Environmental Protection Agency or the National Institute of Environmental Health Sciences) existed much before 1970.

While fluoride research has been dominated by DPH scientists in countries where fluoridation has been actively promoted, work done to support fluoridation is a small part of the total international scientific endeavor on biological effects of the ion. Wide-ranging research has explored dental effects of fluoride, and its potential hazards as an air pollutant, a workplace contaminant, and a natural constituent of water supplies. In India and many other countries, fluoride toxicity from naturally fluoridated water is a major public health problem.

Most of that research approaches fluoride from EH perspectives, and could be very useful for appraising the possible health risks of fluoridation. But it has had minimal impact on the fluoridation debate, at least in the United States. Scientific discussion of fluoridation in this country has been dominated by DPH experts, whose objective is promoting fluoridation, not seeking new insights into potential adverse effects. Such research is often cited by “antis” as evidence of potential hazards. Then, political profluoridationists usually try to discredit the work, or to dismiss that research as “irrelevant to fluoridation.”

Few American scientists experienced in EH research have ever sought to study possible effects of fluoridation. The USPHS and other DPH authorities have effectively defined research on this topic as their “turf,” and they have asserted that all relevant questions were answered long ago, giving the impression that fluoride toxicity is an “old” issue. Relatively little funding is available to support such research. And the intense public controversy over fluoridation deters many objective researchers from studying the topic. Few scientists want to do research that is likely to embroil them in an emotional controversy. It is easier to choose other environmental problems to study.

The result is an odd disparity. In most countries, fluoride research is carried out by EH scientists, seeking to protect the public from adverse effects. But in countries where the fluoridation debate has had major impact, research has been dominated by DPH scientists, and the few EH researchers willing to pursue active studies of potential adverse effects of fluoridation are usually also politically active opponents of the measure. The polarized political dispute in those countries has infected the body scientific, and argument permeated
with political advocacy has effectively crowded out objective scientific inquiry on many important questions.

**The Quality of the Evidence**

In the struggle for credibility, described in Chapter 4 of Martin’s monograph, the credibility of divergent “pro” and “anti” interpretations of scientific evidence looms large. The scientific quality of the evidence itself is, thus, a central concern that cannot be avoided here.

The world literature on biological effects of fluoride is enormous. It was said twenty years ago to comprise at least fifteen thousand published reports. That number may have doubled by now. It is not really feasible for any reviewer to summarize — let alone critically appraise — such a body of knowledge in a brief essay. Instead, I will offer some concise and admittedly subjective impressions. For readers who may be reluctant to accept the word of any one “expert” on this vital topic, I will provide references to a few solid review documents for those who may wish to pursue their own assessments.

To simplify the task a bit, I will arbitrarily divide the vast and complex body of fluoride research into seven parts.

- Studies of the dental benefits of fluoridated water
- Other studies on the anticaries effects of fluoride
- Studies of dental fluorosis or mottled enamel
- Studies on the safety of fluoridation, conducted by or for agencies promoting the measure
- Studies suggesting adverse effects of fluoridation, often done by antifluoridation scientists
- Other research on toxic effects of fluoride, usually done by independent scientists with no involvement on either side of the fluoridation controversy
- Reviews of the literature, written from any of these three perspectives: “pro,” “anti,” or noninvolved

**Benefits of Fluoridation**

Research in this category consists primarily of epidemiological studies of two basic types: surveys of dental health in communities with naturally fluoridated water; and demonstration studies in which changes in rates of dental caries associated with artificial fluoridation were assessed. Prototypes of both kinds were done in the United States, and they have been imitated in many other countries (Newbrun 1986a). According to Newbrun, more than one hundred reports of similar studies have been published.

The vast majority of these studies report substantial reductions in the incidence of dental caries where water supplies had around 1 ppm or more fluoride. The commonly quoted figure of a 50 to 60 percent reduction in tooth decay is a rough average of the results reported in some of the prominent early studies.

Many authorities regard the great number of similar studies and the close agreement of their results as overwhelming proof of fluoridation’s large beneficial effects. Nevertheless, these studies are open to many scientific criticisms. Virtually none of the studies had appropriate controls for factors other than fluoridated water that might affect tooth decay rates. A few had contemporaneous controls in the form of nearby unfluoridated cities; but some such control cities were fluoridated during the course of the studies, and, in other studies, changes in decay rates in the control cities went unexplained. With very few exceptions, the investigators knew where the children examined lived, and their expectations might have influenced subjective assessments of decay status. The random design and statistical rigor commonly expected of, for example, drug-efficacy trials, field studies, and epidemiological research, were either impossible or simply absent from most of the fluoridation studies.
The first substantial scientific critique of the fluoridation studies was published by Sutton (1959), and it has never been effectively shown to be in error. Recently, Diesendorf (1986) cited extensive evidence that tooth decay rates have declined substantially both in countries without widespread fluoridation and in those that have fluoridation. He concluded that factors beyond fluoridation are reducing tooth decay, and that reported improvements may have been improperly credited to fluoridation, rather than to more complex, not fully understood multifactorial causes.

In 1989, an American antifluoridation leader, John Yiamouyiannis, obtained unpublished data from a national survey of the incidence of dental caries that was conducted in the mid-1980s by the National Institute of Dental Research (NIDR). Yiamouyiannis’ analysis of comparative tooth decay rates in fluoridated and unfluoridated communities showed no differences, a claim publicized before his paper appeared in a scientific journal (Yiamouyiannis 1990).

In response to the publicity, NIDR scientists argued that Yiamouyiannis had improperly focused on the number of decayed, missing or filled teeth — one of the more widely used indices of decay status in past studies — as his measure of dental caries rates. Using another index — the number of children with no tooth decay at all — the NIDR claimed to see 25 percent less decay in fluoridated cities. The NIDR response was also publicized before its scientific publication (Brunelle and Carlos 1990).

Whether dispassionate scientists, working out of the glare of public dispute, may soon reach consensus on this issue or not, a significant shift in the debate seems to have occurred. The “pro” side now seems to be arguing that, in today’s health environment, fluoridation may be expected to reduce dental caries by up to just 25 percent. Only a year or two ago, the benefit was still commonly claimed to be a 50 or 60 percent reduction. If, in fact, the “best” estimate of benefits is now lower, we may soon look for revised perceptions of the balance between benefits and risks as well.

These critical perspectives on benefits are well within the realm of legitimate scientific debate, and most are substantive enough to be taken seriously. While they do not discredit the hypothesis that fluoridation reduces tooth decay, they do cast serious doubt on the actual magnitude of the caries-preventive effect. A reassessment of this issue seems to be underway at present among experts, even strong advocates of fluoridation.

Other Research on Fluoride’s Anti-Caries Effects

This category includes a great number of animal experiments, clinical trials, and other studies designed to explore the mechanisms of fluoride’s caries-preventive effects, and to support a range of applications of fluoride against tooth decay (Newbrun 1986b). Most of this research has been independent of the political fluoridation controversy and, thus, insulated a bit from the distorting impacts of that dispute.

Without going into detail, I believe this large body of research provides almost indisputable evidence that fluoride is an effective anti-caries agent. That leaves open the issue of how large the effect of community water fluoridation on the incidence of dental caries may be, but it does make the hypothesis that it has no effect at all quite difficult to entertain.

Studies of Dental Fluorosis

Dental fluorosis, or mottling of the tooth enamel, was the first effect of fluoride on dental health to be extensively studied. Epidemiological surveys in naturally fluoridated areas in the 1930s, conducted primarily by H. Trendley Dean of the USPHS, showed a clear-cut dose-response curve, with both the incidence and the severity of dental fluorosis increasing as fluoride
content of a water supply was increased. The relationship was widely confirmed by other investigators and in other countries.

Dean classified cases of dental fluorosis into five degrees of severity, which he named questionable, very mild, mild, moderate, and severe. His studies (and others) show that some dental fluorosis occurs at fluoride levels as low as 0.5 ppm. At 1 ppm — the level typically used for dental caries prevention — Dean found that 10 to 20 percent of children had dental fluorosis of the questionable, very mild or mild stages, which involve white spots or patches on the teeth. At fluoride levels of 2 ppm or more, moderate and severe stages began to appear, and by 5 ppm, the severe stage involving extensive brown stains on the teeth was quite prevalent. Dean’s studies and others showed that dental fluorosis occurs at lower fluoride concentrations in areas with higher average temperatures, presumably because water consumption is greater in hot climates.

In the early years of research, dental fluorosis was considered to be a serious public health problem, and the USPHS initially set a maximum fluoride level of 1 ppm in order to prevent this adverse effect. But as promotion of fluoridation gained momentum, explicit trade-offs were made, accepting the occurrence of some dental fluorosis in return for caries prophylaxis. Dean and others felt that 10 to 20 percent incidence of no more than mild fluorosis was “not objectionable.” This is clearly a value judgment, and many people do find mottling of their children’s teeth quite objectionable.

To support fluoridation, the USPHS adopted revised fluoride standards, setting a range of “optimal” concentrations which varied with annual average temperature in the community, from 0.7 ppm in hot climates to 1.2 ppm in colder ones. The USPHS set twice the optimal level — 1.4 to 2.4 ppm — as the maximum permissible fluoride levels. Although this implies a “safety factor” of 2, there is, in fact, essentially complete overlap between the range desired for dental caries prophylaxis and the range that causes dental fluorosis in sensitive people. The “safety margin” represents a social judgment that the dental damage done by these fluoride levels is acceptable, and not a margin with no damage. In 1985, the U.S. Environmental Protection Agency relaxed the upper limit to 4 ppm for naturally fluoridated communities, arguing that even severe dental fluorosis was acceptable when compared to the costs of defluoridating many small towns’ water supplies.

Although dental fluorosis has been well documented for more than 50 years, current scientific understanding of the effect is inadequate. Three important areas are still uncertain and subject to controversy. The first is the toxicological meaning of this effect. Is dental fluorosis an external sign of general cellular toxicity, unique only in its visibility, while less detectable effects occur in other tissues? Or are the ameloblasts — the cells that lay down the enamel as the teeth grow inside the jaw — uniquely sensitive to fluoride? More exact knowledge of fluoride’s mechanism of action in causing dental fluorosis could shed light on this pivotal point, but the precise mechanism is still not fully understood.

A second debate persists over whether permanently discolored teeth have any adverse psychological effects on a child. Some psychologists assert that they do, at least in severe cases. In the fluoridation debate, “pros” deny health implications of dental fluorosis, calling it “merely a cosmetic effect.” Some even say that mildly mottled teeth are more attractive. These are obviously subjective judgments, and not scientific conclusions.

The final unresolved issue about dental fluorosis is whether its incidence is increasing. A general increase in exposure to fluoride in the diet has been documented over recent decades, and is attributable to the use of fluoridated water in food processing. If total fluoride intake has increased, dental fluorosis should be more prevalent now than it was before fluoridation. Several studies suggest that it is. For instance,
Leverett (1986) found dental fluorosis to be 3.5 times as prevalent in non-fluoridated communities and twice as prevalent in fluoridated communities as Dean had observed.

Many experts, including some pro-fluoridation leaders, have suggested that definitions of “optimal” fluoride levels in water should be lowered, to compensate for increased dietary fluoride. Other “pros,” understandably reluctant to take a step that would suggest that the margin of safety in current fluoridation levels has been inadequate, have highlighted the uncertainties in the comparisons and called for further study of the question (Szpunar and Burt 1987). This debate has gone on with no major effort to resolve it for some twenty years.

**Studies of the Safety of Fluoridation**

This body of evidence consists of research conducted by or for the USPHS as part of its program to demonstrate the safety of fluoridation. Most of these studies were conducted between 1940 and 1960. Some involved clinical examinations of people in communities with fluoridated water, usually adults with lifelong exposure to naturally fluoridated water. Others were statistical studies of mortality, looking for differences between death rates from major causes in cities with high- and low-fluoride water supplies. In general, the studies reported no evidence of significant adverse effects. Collectively, they are interpreted by both their authors and other proponents of fluoridation as convincing evidence that there are no adverse health effects of any kind associated with fluoridated water (McClure 1962).

Many valid scientific criticisms of these studies have been published. The total number of studies is small — no more than a few dozen. The clinical studies inevitably examined small numbers of subjects, rendering statistically insignificant even those clear-cut differences in health status that were recorded in several studies. Broader statistical surveys looked only at a few major types of toxicity that fluoride might possibly cause. Neither the clinical studies nor the statistical surveys specifically looked for several kinds of adverse effects that other literature clearly attributes to fluoride.

Many of the studies had obvious methodological weaknesses. For instance, a clinical study of children in Newburgh, N.Y., excluded all subjects who had shown any signs of illness. A survey of autopsy data seeking evidence of skeletal fluorosis excluded every individual known to have suffered from any kidney disease. Because renal insufficiency increases retention of fluoride, and, thus, enhances the risk of skeletal fluorosis, the study excluded those people most likely to show the effect it presumably was seeking.

This research was done before modern criteria for assessing the effects of environmental agents were developed. Most studies looked only for obvious clinical symptoms of health damage, not for the subtler biochemical and physiological changes that are now recognized as precursors of frank impairment. No research specifically focused on subpopulations likely to be at higher-than-average risk, such as people with kidney disease or those with extreme water intake. Judged by the standards of modern environmental health research, these studies were poorly conceived, insensitive, and unlikely to find adverse effects even if some were present.

The studies also had an obvious potential for bias because they were sponsored by an agency and carried out by a handful of scientists who were simultaneously engaged in vigorous political promotion of fluoridation. In my judgment, serious actual bias was present. The authors of the studies consistently interpreted incomplete data and ambiguous findings as persuasive evidence of the absence of risk, and they uniformly rejected every result that suggested potential harm as “clinically insignificant” or “not attributable to fluoride.”

In short, the USPHS set out to prove a null hypothesis — that fluoridation could never harm anyone — and perhaps it was politically
necessary for them to attempt that impossible task. Even a much larger body of high-quality studies could not absolutely prove safety. The existing studies are certainly much less than conclusive evidence on the question.

Studies Showing Adverse Effects of Fluoridation

This category includes a variety of published reports — many in well-respected, peer-reviewed journals — which are often cited by “antis” as evidence that fluoridation has harmed or could harm some people. Among them are:

- Clinical reports by several authors (Waldbott and others) of reversible illness, interpreted as a toxic response by hypersensitive individuals to small doses of fluoride;
- Case reports of skeletal fluorosis, including several from the American literature, attributed to drinking water with relatively low fluoride content of 2 to 5 ppm;
- Clinical reports of illness and mortality in patients who were treated by hemodialysis with fluoridated water;
- Statistical analyses suggesting an association between fluoridated water and an increased risk of cancer, and a few animal bioassays for carcinogenicity;
- Epidemiological surveys suggesting an association between fluoridated water and an increased risk of Down’s syndrome;
- Cellular and animal studies on the mutagenicity of fluoride; and
- Animal studies suggesting adverse effects of fluoride on kidney function, enzyme activity, or other processes.

In general, most of these studies are of adequate scientific quality to be taken seriously. Most have no fatal methodological weaknesses or implausible theoretical underpinnings. (NOTE: Some “studies” cited by the “antis” may indeed be disreputable, but it is important not to tar all such evidence with the same brush.)

This research is certainly subject to scientific criticism on many grounds. Some studies do have methodological weaknesses that raise doubts as to their accuracy, and probably should not be accepted as valid unless confirmed by more, better-designed research. Other studies with contradictory findings exist on most of these issues, feeding debates about the relative merits of each study and where the weight of the evidence lies. Some reports, such as in vitro mutagenicity studies, may be accepted as valid, but their implications in terms of potential effects of fluoridation on human health are subject to wide uncertainty and varied interpretations.

None of these studies prove conclusively that fluoridation is harmful, but some provide strong evidence that some effects in sensitive people may be likely. Others raise questions that have not been aggressively pursued by research. Indeed, several authoritative independent scientific reviews identified lists of important questions about the safety of fluoridation that still require further research (National Research Council 1977; Marier and Rose 1977; Taves 1979; and Johnson et al. 1979.)

Other Research on Toxic Effects of Fluoride

This category includes a large body of occupational health research, veterinary studies assessing effects of fluoride air pollution, and epidemiological research on populations in other countries such as India, where an estimated one million people have skeletal fluorosis (Teotia and Teotia 1984).

Most of this research is of average, acceptable scientific quality, and some of it is much better than that. The Indian studies of skeletal fluorosis, for example, include hundreds of papers published over a fifty-year period. The research has documented dose-response curves showing a clear risk of skeletal fluorosis even at 1 ppm fluoride in water. It also identified several stages of the disease, including the subclinical changes that precede the obvious symptoms of
damage; elucidated mechanisms; identified nutrients and other variables that modify risk for individuals; and identified populations at special risk, including children and people with impaired kidney function.

This research — and much other work on related topics — could be enormously valuable for assessing the risk of skeletal fluorosis and other health effects in the United States and other countries with fluoridated water supplies. But it has been largely ignored in the fluoridation debate.

Most scientists who strongly support fluoridation have generally been unwilling to acknowledge the many implications in such research that water fluoridated at 1 ppm poses actual risks to the public. “Pros” often dismiss the Indian studies and similar research as “irrelevant to fluoridation.” Some misrepresent the evidence, asserting, for instance, that skeletal fluorosis in India has been observed only where water contains 10 ppm fluoride or more. The few “antis” who are competent to evaluate the world literature critically have not been able to focus scientific discussion on this research.

**Scientific Summaries and Reviews**

Given the vast amount of primary literature on effects of fluoride, few people can study it all. Reviews and summaries that interpret the literature — and sometimes, reviews of reviews — are, thus, the predominant source of information for people who want to learn more about the scientific evidence.

Unfortunately, reviews of literature relevant to fluoridation reflect the extreme polarization of both the political and scientific debates that has long characterized the controversy. There are many profluoridation reviews (Newbrun 1986b; McClure 1970; and Royal College of Physicians 1976), and a few competent antifluoridation reviews (Waldbott 1965; Waldbott et al. 1978; and Burgstahler 1965). The “pro” reviews appear widely in dental and medical journals, as well as in books, while most “anti” reviews have been published as books, for reasons explored in chapters 4 and 5 of Martin’s monograph.

A reader new to the issue who has not studied the original papers could be seriously misled by the normal assumption that reviews are reasonably objective. One is more likely to make such assumptions about “pro” reviews, because of their respectable trappings, than about more openly biased “anti” tracts. In fact, however, the “pro” reviews are every bit as slanted and distorted as the “anti” ones — and some are worse.

Reviewers on each side are extremely selective, and selectively critical. They cite studies that support their point of view uncritically, often implying — and sometimes asserting — that no contrary evidence or alternative interpretations exist. They bring up studies that the other side cites only to criticize them, and they sometimes misrepresent the evidence in such studies in order to discredit it.

There are some exceptions to this general picture. A few comparatively objective and scientifically credible reviews seek a balanced scientific perspective on the data, rather than to give advantage to one side or the other in the political dispute. Examples include Jolly et al. (1973), National Research Council (1977), Marier and Rose (1977), Taves (1979), Johnson et al. (1979), Dementi (1980), Franke (1979), and Teotia and Teotia (1988).

**Summary**

The overall quality of the evidence on the health effects of fluoridated water is fairly typical of the evidence on many other environmental health issues. There are good studies and bad studies; questions that have been well answered and others that have been barely answered at all; a great deal of evidence of potential risk but little conclusive proof of harm; and nothing like conclusive proof of safety for various populations using water with 1 ppm fluoride over a lifetime. Substantial scientific uncertainty on
most questions makes a range of interpretations possible and precludes absolute answers.

While the scientific picture on fluoridation is typical of science on most such issues — except that many key studies were done a long time ago — the extreme political controversy over social policy in this case has pervaded the scientific debate. That makes objective assessment of this evidence extraordinarily difficult, even in relation to scientific assessments inherent in other environmental policy disputes.

**WHICH SIDE IS SCIENCE ON?**

Actually, my answer is “Neither side.” Ideally, in disputes over public policy involving risks and benefits of an innovation like fluoridation, society needs science to be a neutral arbiter of facts, not a dogmatic advocate of a single policy choice. Pragmatically, the current state of scientific knowledge on questions related to fluoridation makes science effectively neutral. The evidence as a whole can’t be claimed by either side, try as they will.

In the rhetoric of the political debate, science often seems to be on one side or the other, but it isn’t. Professional scientific organizations that endorsed fluoridation expressed their social preferences as citizens, but endorsements have no intrinsic scientific merit. Scientists who campaign for each side are, likewise, acting as citizens, not merely as experts.

Can nonpartisan science resolve the debate? It’s tempting to think so, but I doubt it. Here’s why.

- Scientific consensus (if it were possible) cannot resolve disputes over value judgments and social priorities.
- The enormous world literature actually fuels debate, rather than defuses it. No one interpretation fits all studies, and advocates of any view can find evidence to support the political position they favor.
- New research will not resolve debates, even on issues where more research is clearly needed. Any new study is certain to include enough ambiguity to allow those who don’t like its results — whichever side that is — to dismiss it as inconclusive, and, thus, sustain their existing beliefs.
- There is no organized demand for objective scientific views on fluoridation. Only the active “pros” and “antis” care passionately about the issue. A balanced “on-the-one-hand-but-on-the-other-hand” scientific discussion helps neither side. Each wants slanted scientific-sounding arguments that will help it win the political debate. Objective scientific voices on the issue — such as those cited earlier — have been drowned out by the clamor of the political battle.
- That same emotional battle keeps most objective scientists, especially environmental health scientists with true expertise, from entering the policy debate. It leaves the field to those whose main goal is political victory, not accurate presentation or advancement of scientific knowledge.

I wish I could be more optimistic about the likelihood that objective scientific inquiry would affect public policy debates over fluoridation. But, in twenty years of watching the controversy, I have seen no signs that leaders on either side — those with the power to change the dynamics of the debate — are willing to alter their time-tested approaches.

Ironically, the “antis,” who are usually portrayed as unscientific, often act more scientifically in the debate, probably because it is politically useful to do so. For instance, they frequently cite the unanswered questions about risks, and call for further research. While most “antis” are not scientists, they may have absorbed the ideas and approaches of the environmental health perspective by observing other debates over toxic substances in recent years. By contrast, the political profluoridation stance has evolved into a dogmatic, authoritarian, essentially antiscientific posture, one that discourages open debate of scientific issues.
As long as the debate remains centered on the political fate of fluoridation proposals, it seems unrealistic to expect it to be more scientific. As Brian Martin’s monograph has effectively documented, even those “antis” who are well-credentialed scientists lack the resources needed to force a change in terms of the debate. Because they have the greatest resources, the “pro” leadership has the greatest control over how the debate is conducted, but they seem locked in a corner, where change may well bring defeat.

The wider scientific community — especially those sectors most concerned with environmental health — does have the resources to affect the debate, but it lacks motivation to become involved. As long as the broader scientific community remains aloof from this dispute, I am afraid history will continue to repeat itself.

REFERENCES


Groth, E. 1973. Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area and Fluoridation of Community Water Supplies. Doctoral dissertation, Department of Biological Sciences, Stanford University, Stanford, Calif.


McClure, F.J., ed. 1962. Fluoride Drinking Waters. Publication No. 825, United States Public Health Service, Bethesda, Md. (A collection of USPHS papers on all aspects of fluoridation from research over a thirty-year period, reprinted in one volume.)


The fluoridation controversy

Academy of Sciences, 369-400. (NOTE: The section on fluoride, written by D.R. Taves, is recommended. Summary sections elsewhere in the volume and written by other authors have a distinct profluoridation bias and conflict with the data on 369-400.)


Appendix
Fluoridation around the world

Beginning in 1987, I wrote to health departments in numerous countries in the world enquiring about fluoridation. My standard letter was as follows:

I am carrying out a social scientific study of the issue of fluoridation of public water supplies to reduce tooth decay. Any information you can provide in relation to the following questions would be most appreciated.
1. What fraction, if any, of the population of your country drinks water to which fluoride is added for the purposes of reducing tooth decay?
2. What fraction of the population drinks water which naturally contains fluoride at a level equal to or greater than that considered optimal for reducing tooth decay?
3. What is your government’s current policy on fluoridation?
4. Does your government promote other uses of fluoride, such as fluoride tablets, fluoride in table salt, fluoride in toothpaste, and topical fluoride treatments by dentists?
I would be grateful to receive any relevant documents or articles you can provide relating to these issues.

I obtained a list of addresses of health departments used by a government body in Australia. This covered 37 countries. For countries not on this list, I wrote to embassies and high commissions in Australia. This covered many further countries. Finally, for some others not covered by either of these procedures, I simply wrote to the Minister of Health in the capital city of the country concerned. In countries from which I received no official reply, I also wrote to a few individuals whose names were given to me as likely sources of information.

I did not try to contact every government in the world, but concentrated on industrialized countries and the larger Third World countries.

In the following tabulation, and in the interests of accuracy, I have often closely paraphrased replies received. Some replies did not provide answers to all my questions. This accounts for missing information in what follows. Population figures are for 1986 unless otherwise stated. Additional information has been used when available and useful.

For some countries, a few further English-language references dealing with fluoridation or the fluoridation controversy are listed.

General sources
Frank, R.M. and S. O’Hickey, eds. Strategy for Dental Caries Prevention in European

Australia
Population, 15.6 million in 1984

1. 10.2 million or 66 percent drank water with added fluoride.
2. About 136,000 or 0.9 percent drank naturally fluoridated water (0.5 ppm fluoride or more).
3. The National Health and Medical Research Council has supported fluoridation in a series of statements since 1952. Decisions about fluoridation are made at the local level.

Source

See also

Australia
Population, 7.6 million in 1984

1. No water supplies contain added fluoride.
2. About 15,000 or 0.2 percent drink water naturally containing 1 ppm fluoride or more.
3. Fluoride tablets are provided to the public.

Source
Letter from Erich Klaus, Secretary Administration, Austrian Embassy, PO Box 375, Manuka ACT 2603, Australia, dated 6 August 1987.

Belgium
Population, 9.9 million

1. No water supplies contain added fluoride.
2. About 100,000 or 1 percent drink water naturally containing 1 ppm fluoride or more. Most drinking waters have less than 0.5 ppm fluoride.
3. Local or regional authorities make the ultimate decisions about fluoridation.
4. The government promotes other uses of fluoride mainly through treatment in medical schools and through general recommendations on dental hygiene.

In the 1950s, there was a limited trial of water fluoridation in a community with a population of about 8,000. It was discontinued for a variety of reasons, one of which was probably economics.

Source

**Brazil**
Population, about 124 million in 1982

1. Approximately 26 million or 21 percent drank water with added fluoride.
2. Naturally fluoridated water is rare.
3. Oral health is a priority area for government assistance, and fluoridation is being promoted.
4. Fluoride toothpastes are used widely. Other fluoride vehicles are used on a limited scale, including topical treatments and mouth rinses in schools.

**Source** Letter from Carol C. Sherman, Science and Technology Section, Embassy of Brazil, GPO Box 1540, Canberra ACT 2601, Australia, dated 29 May 1987.

**Canada**
Population, 23.0 million in 1976

1. Approximately 8.38 million or 36 percent drank water with added fluoride.
2. 174,000 or 0.76 percent drank water with naturally occurring fluoride.
3. Decisions about water fluoridation are taken at a local or regional level. With a few exceptions, formal guidelines for preventive dental services do not exist in Canada, nationally or regionally.


**Chile**
Population, 12.1 million

1. 1.26 million or 10.46 percent drink water with added fluoride. These people live in the Fifth Region of Chile, an experimental area for fluoridation.
2. 1.30 million or 10.81 percent drink water with naturally occurring fluoride at a level considered to be “fairly acceptable,” although not optimal.
3. The government’s National Program of Fluoridation of Drinking Water Supplies began with fluoridation of Fifth Region water supplies. This program will be expanded to cover other regions, subject to budgetary considerations.
4. The Ministry of Health encourages the use of fluoride in regions where the water does not contain added or natural fluoride. The Ministry of Health runs programs for schools that include topical fluoride treatments, as do dental practices that are part of the National Health Services system. Most toothpastes contain fluoride.

**Source** Letter from Guillermo Anguita, Second Secretary, Embassy of Chile, PO Box 69, Red Hill ACT 2603, Australia, dated 18 August 1987.

**Czechoslovakia**
Population, 15.5 million

1. In 1987, about 3.3 million or 21 percent drank water with added fluoride. In 1988, fluoridation ceased in Ceske Budejovice and Prague.
2. There is one locality with a natural fluoride level higher than permissible. (The World Health Organization guidelines for Czechoslovakia’s climate specify 0.8 to 1.5 ppm.) The water in this locality is diluted with water from other sources.
3. The Scientific Board of the Ministry of Health established the Fluoride Committee to regulate the use of fluoride in drinking water. This committee brings together experts from all fields considered to be relevant. Fluoridation is recommended wherever it is deemed effective and suitable. It is not compulsory. If...
it is recommended by the environmental and health services, it still requires the consent of regional or local authorities.

4. In places where fluoridation is not suitable, sodium fluoride tablets are provided if approved by appropriate medical officers. Fluoride toothpastes are available for purchase.


Denmark
Population, 5.1 million

1. No water supplies contain added fluoride.

2. Some 150,000 to 300,000 or 3 to 6 percent drink water that naturally contains fluoride.

3. The Minister for the Environment, Helge Nielsen, stated on 5 January 1977 that water fluoridation should not be allowed. Factors involved in formulating this opinion included:
   • the cost of fluoridation, considering variations in fluoride levels in groundwater (the major source of the water supply);
   • possible impacts of fluoride on plants and animals in marine and fresh waters;
   • the narrow interval between the levels of fluoride causing beneficial and harmful effects; and
   • possible overdosing of critical groups, including people drinking very large amounts of water, people with reduced kidney function, people undergoing prolonged dialysis, and babies fed with foods using dried milk.

4. Several uses of fluoride are promoted, especially fluoride toothpastes, rinses, and topical treatments, and, to a small extent, fluoride tablets and varnish.

Sources Letter from Eli Schwarz, Chief Dental Officer, National Board of Health, 1 St. Kongensgade, DK-1264 Copenhagen K, Denmark, dated June 1987; “Fluoridation of drinking water.” Nyt fra miljøstyrelsen. special issue (February 1977).

See also


Fiji
Population, 714,000

1. Only the population of Suva — 71,000 or 10 percent — drinks water with added fluoride. Even so, there are often long periods during which the water in Suva is not fluoridated due to mechanical problems.

2. There is no evidence that Fiji waters contain any natural fluoride.

3. Although the government has no formal policy, it encourages the use of fluoride.

4. All methods of using fluoride are promoted except for fluoride in salt.


Finland
Population, 4.9 million

1. Only the population of Kuopio — 76,000 or 1.6 percent — drinks water with added fluoride.
2. About 200,000 or 4.1 percent drink water with natural fluoride.
3. The government supports fluoridation but has not been very active in promoting it.
4. The government promotes fluoride tablets, toothpastes, and topical treatments, all of which are widely used.

Source Letter from Dr. Heikki Tala, Assistant Chief Dental Officer, National Board of Health, Siltasaarenkatu 18 A, PB 223, SF-00531 Helsinki 53, Finland, dated 27 May 1987.

See also

France
Population, 55.2 million

1. No water supplies in France contain added fluoride.
2. Probably about 940,000 or 1.7 percent drink water with fluoride naturally at an adequate level between 0.7 and 1.5 ppm, and about 260,000 or 0.5 percent drink water with fluoride naturally at a possibly hazardous level greater than 1.5 ppm.
3. Fluoridation has not been undertaken because French consultative representatives considered that the large number of distribution plants (more than 20,000) and great regional variations in fluoride concentrations present technical difficulties that cannot be overcome.
4. In 1985, the law was changed to allow fluoridation of milk and of table and cooking salt for a period of five years. Fluoride toothpastes and tablets are sold only in pharmacies.


German Democratic Republic (East Germany)
Population, 16.6 million

1. Roughly 3.4 million or 20 percent drink water with added fluoride.
3. Karl Marx Stadt was fluoridated in 1959. When technically feasible, water fluoridation is the method of choice for preventing tooth decay, and is part of the government’s national health program.
4. The national health program also includes provision of fluoride tablets, topical treatments, and recommendations for using fluoride toothpastes.


Federal Republic of Germany (West Germany)
Population, 60.7 million

1. No water supplies contain added fluoride.
3. Sources differ as to whether fluoridation is legally permissible. According to the Minister of Youth, Family, Women, and Health, fluoridation is not allowed because there are people who must or prefer to drink unfluoridated water whereas, according to commen-
tator H. Pohl, water fluoridation is possible. In any case, there is no fluoridation anywhere in the country, partly due to the activities of antifluoridationists. The city of Kassel was fluoridated from 1952 to 1971.

4. Addition of fluoride to foodstuffs, such as salt or milk, is illegal. The federal government encourages the use of fluoride toothpastes and tablets.


Greece
Population, 10.0 million

1. No water supplies contain added fluoride.
2. About half the rural population drink water naturally containing 1 ppm fluoride or more. Drinking water in urban areas usually has less than 1 ppm.
3. The issue of government policy on fluoridation does not arise because the major relevant health problem is endemic fluorosis. Defluoridation plants and deep bore water supplies have been introduced to provide drinking water with less than 1 ppm fluoride.
4. Apparently there is no government policy permitting the use of fluorides. Fluoride toothpastes and topical treatments are used in some areas.


Iran
Population, 49.9 million

1. No water supplies contain added fluoride.
2. Sixteen million or 34 percent drink water naturally containing 1 ppm fluoride.
3. The government plans to introduce fluoridation in urban areas, and also to introduce fluoridated table salt.
4. Some physicians prescribe fluoride tablets, some toothpastes contain fluoride, and some dentists give topical fluoride treatments.

Source Letter from Ahmad Attari, Ambassador, Embassy of the Islamic Republic of Iran, 14 Torres Street, Red Hill ACT 2603, Australia, dated 25 September 1987.

Ireland
Population, 3.5 million

1. 2.3 million or 66 percent drink water with added fluoride.
2. The Minister of Health can direct health authorities to add fluoride to water supplies under the Health (Fluoridation of Water Supplies) Act of 1960. A legal challenge to this act failed in both the High Court and the Supreme Court in 1964. Fluoridation in Ireland is compulsory and national. All major centers of population were receiving fluoridated water by 1969. The third of the population not receiving fluoridated water live in rural areas and small towns.
3. Almost all toothpastes contain fluoride, most dentists use topical fluorides, and there are some programs for using fluoride mouth rinses and tablets.

Sources

Israel
Population, 4.3 million

1. Approximately 870,000 or 20 percent drink water with added fluoride.
2. About 108,000 or 2.5 percent drink water with fluoride naturally at a level considered to be satisfactory.
3. The current policy of the Ministry of Health follows the guidelines of the World Health Organization.
4. The Ministry encourages a range of fluoride vehicles, such as tablets, toothpastes, rinses, and topical treatments.


Japan
Population, 121.7 million

1. No water supplies contain added fluoride.
2. Of the 1972 population served by community water supplies, 0.4 percent drank water with fluoride at 0.8 ppm or more.
3. The government does not permit water fluoridation. The water quality standard for fluoride was set in 1978 by the government at less than 0.8 ppm.
4. No uses of fluoride are promoted by the government. The use of fluoride toothpastes is widespread, and some dentists use topical fluoride treatments.

Scientific knowledge in controversy

Source Letter from Humio Tsunoda, Professor and Director, Department of Hygiene and Public Health, Iwate Medical University, 19-1, Uchimaru, Morioka, 020 Japan, dated 31 March 1989.

Lebanon
Population, 2.7 million

1. No water supplies contain added fluoride.
4. Dentists recommend fluoride toothpastes, which are widely used. Pharmacies stock fluoride tablets.

Source Letter from the Embassy of Lebanon, 73 Endeavour Street, Red Hill ACT 2603, Australia, dated 10 December 1987.

The Netherlands
Population, 14.5 million

1. No water supplies contain added fluoride.
2. No water supplies contain fluoride naturally at 1 ppm or higher. The maximum natural level of fluoride is far below this.
3. There is no intention by the government to introduce fluoridation. Earlier, there was widespread fluoridation, but following efforts by anti-fluoridationists, the Supreme Court of Justice ruled in 1973 that the Water Supply Act was not an acceptable legal basis for it. Legislation prepared to legalize fluoridation was withdrawn from Parliament in 1976 to avoid its rejection and there has been no fluoridation since that time.
4. All uses except fluoride in table salt are promoted. Ninety percent of toothpastes sold are fluoridated. Topical fluoride applications and fluoride tablets are paid for by social insurance.


New Zealand
Population, 3.3 million

1. About 1.65 million or 50 percent drink water with added fluoride.
2. Naturally fluoridated water is found in only a few very small water supplies.
3. Fluoridation has been endorsed by the Department of Health as a “proven health measure” and as the single best community-based method for preventing tooth decay.
4. The Department of Health recommends: the use of fluoride tablets for children older than six months of age in areas where the water supply has less than 0.3 ppm fluoride; the use of fluoride toothpastes by all people; and that dentists and school dental nurses should consider topical fluoride treatments for individual patients.

Sources Letter from Peter B. V. Hunter, Department of Health, PO Box 5013, Wellington, New Zealand, dated 8 June 1987; Clinical Services Letter No. 222, Department of Health, Wellington, dated 14 September 1983.

See also


**Norway**

Population, 4.2 million

1. No water supplies contain added fluoride.
2. About 22,000 or 0.53 percent drink water with fluoride naturally between 0.50 and 0.74 ppm; 8,300 or 0.20 percent drink water with fluoride naturally between 0.74 and 1.99 ppm; and about 6,200 or 0.15 percent drink water with fluoride naturally at unfavorably high levels between 2 and 5 ppm.
3. For fluoridation to become possible, a resolution would have to be introduced in the Norwegian parliament. This has not happened. Currently, there is no political interest in fluoridation, primarily because of public resistance. On the other hand, Norwegian health authorities support fluoridation, in agreement with the World Health Organization.
4. The Public Dental Health Service has made widespread use of different fluoride vehicles such as tablets and rinses. In 1985, 70 percent of toothpastes sold contained fluoride. In most parts of the country, children receive fluoride tablets at no cost.

*Source* Letter from Ole W. Sandbekk, Assistant Deputy Director General, and Bente Traeen, Executive Officer, Directorate of Health, PO Box 8128 DEP, N-Oslo 1, Norway, dated 30 June 1987.

See also


**Papua New Guinea**

Population, 3.4 million

1. Only the people in Port Moresby (population approximately 250,000 or 7.4 percent) drink water with added fluoride.
2. There is very little information available on natural levels of fluoride in the water.
3. In 1965, the government passed legislation requiring fluoridation of public water supplies at the level of 0.8 ppm. Due to a shortage of qualified personnel, only the city of Port Moresby has been fluoridated.
4. Outside Port Moresby, dental workers are encouraged to provide fluoride tablets and topical treatments. Flouride toothpastes are promoted, but not fluoride in table salt.

*Source* Letter from Dr. Bais Gwale, Coordinator of Dental Health Services, Department of Health, PO Box 3991, Boroko, Papua New Guinea, dated 4 August 1987.

**Philippines**

Population, 58.25 million

1. About 8,300 or 0.014 percent of the population drink water with added fluoride. Only the United States military bases have fluoridation.
2. About 4.5 million or 7.72 percent drink water naturally containing fluoride at or above the level considered optimal for reducing tooth decay, which, in the Philippines, is 0.4 to 0.6 ppm.
3. The Fluoridation Law of 1963 authorized the fluoridation of public water supplies. In 1980, an installation to fluoridate metropolitan Manila was initiated, but it has not been completed due to political and financial difficulties. Small pilot projects were started in Limay, Bataan, and San Jose City, but were stopped for the same reasons.
4. The government promotes fluoride mouth rinsing every two weeks. Fluoride toothpastes are widely sold. The government has not yet
promoted fluoride tablets or fluoridated table salt. Topical fluoride treatments at rural dental clinics were too expensive in terms of staff and so were phased out.


**Poland**
Population, 37.5 million

1. Less than one million or 2.7 percent drink water with added fluoride.
2. About 200,000 to 300,000, or 0.5 to 0.8 percent, drink water naturally containing fluoride at a level equal to or greater than that considered optimal for reducing tooth decay.
3. The government supports fluoridation, but there are obstacles to it in particular provinces, some due to antifluoridationists.
4. The government promotes fluoride tablets, toothpastes, and topical treatments.

*Source* Letter from Prof. Dr. hab. Zbigniew Jacńzuk, Pomorska Akademia Medyczna, Stomatologii Zochowawczej, Al. Powstańców W kp. 72, blok 18, 70-111 Szczecin, Poland, dated 31 July 1987.

**Portugal**
Population, 10.3 million

1. Only the small town of Montemor-o-Novo (population approximately 20,000 or 0.2 percent) drinks water with added fluoride.
3. The extension of fluoridation nationally is being studied.
4. Since November 1985, there has been a program of fluoride tablets for children of kindergarten age and regular periodic fluoride mouth rinses for pupils in elementary schools. In 1987, a national program of oral health education began which includes a recommendation to use fluoride toothpastes.


**Romania**
Population, 22.7 million

1. No water supplies contain added fluoride.
2. About 4.5 million or 20 percent drink water naturally containing an optimum fluoride level of more than 0.5 ppm.
3. The city of Tîrgu Mureș was fluoridated for over a decade from 1961, but this was terminated due to economic reasons.
4. Government authorities support the use of a number of fluoride vehicles. Fluoride toothpastes, mouth washes, and gels are for sale.

*Source* Letter from Dumitru Tănăsel, Director, Ministerul Sănătății, Str. Ilfov No. 6 – Sectoral VI, 70621, Section 5, Bucharest, Romania, dated 31 October 1987.

**Singapore**
Population, 2.6 million

1. Since 1958, all of the population drinks water with added fluoride.
2. None of the population drinks water with natural levels of fluoride.
3. The government supports fluoridation.
4. Other uses of fluoride are not promoted actively by the government. Fluoride toothpastes make up almost all of the market. Dentists are free to offer topical fluoride treatments.

*Source* Letter from Miss Tan Bee Lian, Public Relations Officer, Ministry of Health, 55 Cuppage Road, Cuppage Centre #09-00, Singapore 0922, dated 16 June 1987.
South Africa  
Population, 23.2 million

1. No drinking waters contain added fluoride.  
3. The Health Act, 1977, allows the Minister of Health to regulate for the introduction of fluoridation, but this has not yet happened. The Department of Health is currently investigating fluoridation due to increased interest in South Africa. Principles to be considered in drafting regulations include the following:  
• A local authority, responding to public opinion, must first assess fluoridation itself. Then, it can apply to the Department of National Health and Population Development for approval.  
• Having received an application from a local authority, the Department may permit fluoridation under specified conditions, but it will not be compulsory.  
4. The government neither promotes nor discourages other fluoride vehicles. Fluoride toothpastes and tablets are available for purchase.


Sweden  
Population, 8.4 million

1. No drinking waters contain added fluoride.  
2. In 1977, about 750,000 or 9 percent drank water naturally containing 0.8 ppm fluoride or more.  
3. The Water Fluoridation Act of 1962 made it possible for municipalities to seek permission for local fluoridation. Of the nine towns and several rural districts that were granted permission, none had yet implemented fluoridation before the Water Fluoridation Act was withdrawn in 1971. In 1977, a parliamentary committee, the Fluoride Commission, was appointed to consider the issue. The Fluoride Commission opposed legislation permitting fluoridation, on the grounds that tooth decay had declined due to other measures and further preventive effects could be obtained voluntarily. The Commission noted that many people believe fluoridation is an encroachment on the individual’s freedom of choice and noted that long-term environmental effects of fluoride are not well enough understood. The Minister of Health in 1985 declared that the government did not intend to raise the issue of fluoridation again.  
4. Fluoride toothpastes with fluoride concentrations of less than 0.15 percent are available without prescription and constitute more than 80 percent of the market. Fluoride mouth rinses require a prescription if they contain more than 0.025 percent sodium fluoride. Fluoride tablets, which contain 0.25 mg fluoride, can be obtained only with a dentist’s prescription.

Sources  
Switzerland
Population, 6.5 million

1. Only the people in Canton Basel-City (population about 200,000 or 3 percent) drink water with added fluoride.
2. There are only rare cases (2,000 to 3,000 people or 0.03 to 0.046 percent) where the drinking water naturally contains fluoride at 1 ppm or more.
3. Decisions about fluoridation are made by local authorities. There are two main reasons for decisions against water fluoridation in a number of cities: economic costs associated with fluoridating complex water supply systems; and the promise of salt fluoridation, in the light of the effectiveness of iodized salt.
4. Except in Canton Basel-City, table salt containing 0.025 percent fluoride is available for purchase. There is also unfluoridated table salt available. In 1982, fluoridated salt made up 72 percent of sales. Fluoride toothpastes (up to 0.15 percent) are available for purchase. Fluoride tablets (0.25 mg) and gels (1.0 to 1.3 percent) are sold only in pharmacies and drugstores.


See also

Thailand
Population, 48.85 million in 1982

1. No drinking water contains added fluoride.
2. About 3.95 million or 8.1 percent either live in an area containing fluoride deposits according to the Department of Mineral Resources, or drink water naturally containing fluoride at an optimum level or greater from 0.70 to 3.01 ppm.
3. The government currently has no policy on fluoridation.
4. The government provides fluoride mouth rinses (0.2 percent sodium fluoride) for all primary schools. It also requires every registered brand of toothpaste to contain fluoride (0.11 percent or less), and it produces fluoride tablets. Dentists individually may provide fluoride tablets, syrup, and topical treatments.


Turkey
Population, 51.8 million

1. No drinking waters contain added fluoride.
2. Of 66 provinces, 15 contain at least some water supplies with fluoride at a level of 1 ppm or greater.
4. No foods contain added fluoride. The Ministry of Health encourages the use of fluoride toothpastes. Dental treatment centers and dental health programs give topical fluoride treatments.

Source Letter from Yucel Ayasli, Counsellor, Turkish Embassy, 60 Mugga Way, Red Hill ACT 2603, Australia, dated 20 April 1987.
**Union of Soviet Socialist Republics**

Population, 275.6 million

1. About 41.34 million or 15 percent drink water with added fluoride, according to World Health Organization figures. Independent testing of water samples in Leningrad and Moscow suggests that fluoridation may be less pervasive or reliable than these figures indicate.

3. The Council of Ministers of the USSR authorized fluoridation throughout the country in 1964. Local decisions are made by the Chief State Sanitary Inspectors of Soviet Republics, taking into account a number of specific factors. The two most important indicators of the need for fluoridation are a fluoride level of less than 0.5 ppm and a high level of tooth decay in children.

**Sources**


Table 1 in Ibid: 5.

**United Kingdom**

Population, 56.5 million

1. Approximately 5 million or 9 percent drink water with added fluoride.

2. Approximately half a million or 0.9 percent drink water naturally containing fluoride near 1 ppm.

3. The government supports fluoridation, believing it to be safe and effective. Nevertheless, the government is also aware of public concern about fluoridation and, as a result, believes that decisions should be taken at a local level rather than nationally. The Water (Fluoridation) Act, which came into effect in 1985, requires local health authorities to undertake extensive public consultations prior to any decision to implement fluoridation.

4. The government supports the use of fluoride toothpastes and, in unfluoridated areas, fluoride tablets and gels. Fluoride in table salt is not supported.

**Sources**


**United States**

Population, 243 million in 1985

1. Approximately 121 million or 50 percent drink water with added fluoride.

2. Approximately 9 million of the 212 million served by public water supplies drink water whose natural fluoride content is at optimal or higher levels.

3. The federal government actively promotes fluoridation, encouraging all communities to adopt it. Decisions are made by local governments. Some states have laws requiring local fluoridation.

4. Fluoride tablets are distributed through school programs and dental clinics. School
water fluoridation is encouraged where community water supplies are not fluoridated. Fluoride toothpastes, mouthwashes, gels, and bottled water are widely available. Topical fluoride treatments by dentists are available at the dentist’s discretion, and there are government-supported programs of topical treatments in schools.

Sources

See also

Zimbabwe
Population, 9.0 million

1. No drinking water contains added fluoride.
2. Projections indicate that perhaps 362,000 or 4.0 percent drink water with natural fluoride equal to or above the optimal level.
3. The government supports fluoridation. Local authorities have responsibility for implementation.
4. The government promotes several fluoride vehicles, aided by the dental association and fluoride toothpaste companies.


Miscellaneous

In addition to European countries already listed, the World Health Organization, in Experience on Water Fluoridation in Europe, Copenhagen: World Health Organization Regional Office for Europe, 1987, gives the following figures on page 5 for the fraction of the population in Europe served by fluoridated drinking water. No sources are given for this data.
- Albania, population 3.0 million, 0 percent
- Bulgaria, population 9.0 million, 0 percent
- Hungary, population 10.6 million, 0 percent
- Italy, population 57.3 million, 0 percent
- Spain, population 38.9 million, 0 percent

Information sought but not received

Letters were sent to health departments with a detailed address in the following countries, with no reply: Bulgaria, Burma, France, India, Indonesia, Italy, Japan, South Korea, Malaysia, Nigeria, Pakistan, Sri Lanka, USSR, United States, and Yugoslavia. Letters were sent to the Australian embassies of the following countries, with no reply: Bangladesh, People’s Republic of China, Cyprus, Egypt, Iraq, Jordan, Mexico, Peru, Spain, Uruguay, Vietnam, and Zambia. The embassies of Argentina, German Democratic Republic, and Kenya replied saying they had requested information from relevant authorities, but no information was received. Letters were also sent to “The Department of Health” in the capital cities of the following countries, with no reply: Albania, Hungary, North Korea, and Uganda.
Scientific Knowledge in Controversy – the Social Dynamics of the Fluoridation Debate

Brian Martin, 1991

Earlier social science studies were commissioned by profluoridation organisations, and written by profluoridation social scientists. This work avoided the question of who was right or wrong regarding the science, and looked only at tactics used.

In this book, the controversy is analysed from the “power picture of science”. Power is involved in all aspects of science, even in the daily processes by which scientists make decisions about what is valid knowledge. This depends on getting agreement from other scientists, and this may involve funding, status, or persuasive ability.

An important concept is interest. Scientists have an interest in obtaining publishable results, establishing a good reputation, and having a good job (cf Mullinex).

An important aspect of the debate is the struggle for credibility. This means going far beyond attacking the credibility of scientific statements, which would constitute part of an intellectual dispute. Rather, the attack is on the credibility of individuals as scientists and as honest sensible and upstanding citizens.

An exercise of power has been the control over publication, research funding, and professional accreditation. In all these areas there are examples of the overt use of the power of the dental profession against antifluoridationists.

The material basis for scientific communication, scientific research, and professional advancement – namely, publications, research grants, and accreditation – have been used as tools in the struggle.

It is impossible to separate the scientific and power dimensions of the issue. To understand the scientific work on fluoridation it is necessary to understand the wider social context – the careers of individuals, the commitment of the USPHS and the ADA, and the potential corporate hostility or support. All of these can influence what scientific research is done or not done, the predisposition of researchers to obtain particular types of results, and the assessment of contrary findings. The body of research relating to fluoridation and the common evaluations made of it cannot be separated from the wider power dimension of the controversy.

In 1952, proponents refused to appear on a radio forum in Washington DC, shortly after the city’s water supply had been fluoridated. The observation: “The professional proponents of fluoridation, as a rule, refuse to discuss the subject in public meetings or debate fluoridation with anyone who opposes it in public forums.” This has remained the pattern ever since.

Ernest Newbrun states “that he normally refuses to debate because “it is my policy not to give credibility to antifuoridationists”

In 1985 Michael Easley : “Regardless of which side is successful in presenting the best argument, the mere fact that the debate even took place conveys to the public that a legitimate scientific controversy exists”.

In 2000 the York Review said “until better quality research is done, there will continue to be a legitimate scientific controversy over fluoridation.”
When fluoridation supporters refuse to debate it is often seen by the public as arrogance.

A response by fluoridation promoters of logical criticism is not always enough to undermine an opponent’s credibility. Ways to neutralise these people are limited. The choices are

- ignore them
- assail their motivations, or
- drown them out by enlisting large numbers of dentists and physicians in a manner highly visible to the public.

The third is, obviously, the best choice.

Antifluoridation science and reviews are often neither quoted nor listed in bibliographies of profluoridation works. If mentioned at all, the specific evidence supporting anti-F claims is rarely discussed. This method of not giving opponents the status of a name or an argument has been used frequently, for example in numerous editorials of the JADA. Attacking the other side in unspecified terms is especially useful for those who have more status, since they avoid giving opponents recognition.

Another technique is the unpublished critique. These are circulated to government officials, newspaper editors etc. The victim of the critique may never know it exists, so cannot rebut it. Yet attitudes are formed and decisions are made on the basis it.

One advantage is that nothing about the issues being contested ever appear in dental journals, and are not raised to the status of being worthy of public debate.

As long as research adverse to fluoridation is not widely known, it is more effective to circulate unpublished critiques. This approach may not be as effective when such research gains widespread publicity. (why not – it still seems to undermine credibility in a way that cannot be addressed, and therefore democratic decision making remains undermined.)

A variation of this is to base a critique on alleged, but unpublished, research. This was used by AL Russell against Ionel Rapaport’s 1950s study showing a link between fluoridation and mongoloid births. [Reviewer’s note: The same technique was used by Douglass and Joshipura against Elise Bassin’s study showing increased osteosarcoma with fluoridation, published in 2006.]

Another approach is to associate opponents with discredited persons.

The technique of attacking credibility has been overwhelmingly more effective for promoters as they have had the preponderance of professionals, and the weight and resources of professional associations.

**Professional attacks**

Dentist Ivan Northfield, Dukuth, Nth Minnesota, made a speech against fluoridation during a 1965 campaign. His license was suspended for a year. He was not allowed to speak in his own defence.
Dr Chang had researched and documented harm from fluoride while working at University of California and US Department of Agriculture. The USDA demanded he only research in areas not related to fluoride.

Carol Farkas gave a talk to the Canadian Dental Association on her research showing that some people might be ingesting too much fluoride. After the talk several dentists asked for her phone number. 5 of them called, saying that they agreed with her but could not say so in public because they would be blackballed from the CDA.

Owen Hooton, a respected Auckland dentist, publicly dissociated himself from the push for fluoridation. He was visited by an officer of the Dental Association, who told him to stop disagreeing with his colleagues in public. He then made the public statement: “The majority of people are against fluoridation [based on 10 referenda]. The methods being used by both the Health Department and the NZDA to force this issue are repugnant to me.”

The combination of attacks at all levels discourages many scientists from doing research on adverse effects of fluoridation, or speaking of their findings publicly if they do. The consequent relative lack of open opposition then encourages a perception of the “fringe” position of critics.

In 1962 a conference on fluoride toxicology was held in Bern, Switzerland. A publisher of medical and dental literature typeset the book written on the proceedings. The Dental profession threatened to boycott his company if he proceeded, and paid him compensation for withdrawing from publication.

Leading scientist opponents attract a disproportionate share of attacks because it is especially important to reduce the effectiveness deriving from their greater credibility.

Profession is a way of organising an occupation to gain and protect wealth and status.

Dental researchers who have built a reputation on research into and support for fluoridation constitute one group with a clear career and personal interest in promoting fluoridation.

An analysis of fluoridation promotion in terms of interests does not depend on the motivations of individuals. It depends on the existence of some benefit, material or symbolic, accruing to individuals or groups. Hierarchies of associations and govt departments provide opportunities for individuals to gain in terms of income, status, and power. Promotion of fluoridation is one path to these benefits.

Dental students are more often taught “the correct view” than taught to make a critical and independent assessment of the evidence and arguments. In NZ, medical and dental students are told never to question fluoridation.

Another factor is the image of the dental profession as a whole. The power and status of the medical profession was immensely improved by the discovery of antibiotics and other “wonder drugs”. None of the advanced techniques adopted by dentistry can claim to have caused the miraculous reduction in dental problems. Fluoride is the best candidate for dentistry’s claim to a scientific breakthrough. The research was done by dentists. This mimics the established pattern of medical breakthroughs. This represents dentistry’s most distinguished claim of contribution to improving the public’s health. The Australian Department of Health states
“Fluoridation of water is perhaps the greatest single development in the history of dentistry”.

Fluoridation thus provides the basis for an elevation of the public image of the entire dental profession. As with medicine, it doesn’t matter if fluoridation actually works or not. What is important is that most dentists think it does, and have been able to convince the public.

Isn’t it against dentists’ interests to reduce tooth decay?

Answer: No.

Doctors were not put out of business by antibiotics and vaccines.

There are at least three reasons why reduction in tooth decay is not threatening to dentists:

1. There were never enough dentists to start with
2. Entry is limited
3. Dental practices are changing toward more labour-intensive cleaning and restoration

[Reviewer’s note: I could also add:

1. Reducing tooth decay does not reduce the need for regular dental treatment
2. In the US and Canada treating dental fluorosis employs more dentists than treating tooth decay
3. In early times, people had all their teeth out by early to mid twenties – no more work for dentists. Today, people keep their teeth – maybe 50 or 60 years more maintenance work for dentists
4. With a more affluent society, people can afford expensive work to keep their teeth, and keep them looking good.]

There is a small number of promoters, especially researchers, who have built their careers on fluoridation. They have their reputations as well as many years of personal commitment at stake.

Fluoridation is the only measure that has increased the status of dentistry as a profession. Since the dental profession made a strong commitment to fluoridation it staked its reputation on the measure. It became very difficult to reverse or even modify the policy, because this would be tantamount to admitting that the dental experts were wrong – both ethically and scientifically – in promoting an insufficiently tested procedure.

It is extremely difficult to modify a policy that has long been defended in a highly polarised situation.

Fluoridation was vital to the careers of some researchers and to the image of the dental profession as a whole. It just so happens that the proponents of fluoridation were able to capture control of the professional resources of the US and other countries. These resources – including access to professional journals, membership
of dental associations, and availability of research funds — were then used in the struggle against opponents.

It has been vital to the success of fluoridation to capture control of the dental profession, because its resources were so powerful. The early efforts by “the Wisconsin dentists” (Frisch and Bull) and other proponents to obtain endorsements from the USPHS, the ADA, and AMA were crucial. It has subsequently been vital to maintain the appearance of professional unanimity. As long as opponents have no scientific or professional credibility, they can more easily be typecast as unknowledgeable cranks, and thus rejected. This strategy has depended on discouraging professionals from taking vocal open stands against fluoridation.

As well as adding status to certain groups, supporting fluoridation also avoided conflict with powerful corporate groups, such as the sugar industry, and wider food industry. There is a massive industrial interest in promoting selling refined carbohydrates. Meanwhile, there is no substantial industrial group opposing fluoridation. There does not appear to be a deliberate collusion — it just avoids the dental profession being in conflict with those who could damage it.

In the US, public officials were much easier to convince than the public. This led to a strategy of approaching public officials behind the scenes while avoiding public debate.

Bureaucracy is a type of political system. Bureaucracies typically have an “old guard” committed to long-established policies.

Conversely, opposition to fluoridation is not easily explained in terms of money, power, or prestige to be gained by identifiable groups.

Proponents had enormous early success winning key government and professional bodies over to their side. They then used the power of these organisations to marginalise opponents and persuade communities to the pro-fluoridation view.

Due to the agenda set by promoters in the 1940s, opponents were forced to take a defensive “anti” position. It was never clear what they were for. Any positive position on tooth decay gets lost in the passion of the debate. If opponents were active in other positive campaigns they would have far greater credibility.

The use of “front organisations”.

An example is the American Council on Science and Health (ACSH), which describes itself as “a national consumer education association directed and advised by a panel of scientists from a variety of disciplines... committed to providing consumers with scientifically balanced evaluations of issues relating to food, chemicals, the environment and health.”

ACSH is heavily supported by corporate donors, including many manufacturers of sugary foods. It prepares reports on a wide variety of topics, almost always taking a position congenial to corporate interests. Its report on fluoridation is strongly supportive.
Some of the members of ACSH’s Board of scientific advisors are ardent fluoridation proponents. One pro-fluoridationist received significant research grants from the sugar industry for fluoridation research.

Commentary by Edward Groth III – which side is the science on?

Groth is a biologist who has specialised in the study of policy decision-making processes on environmental and public health issues. He has a PhD in Biological Science from Stanford University.

While science can measure risk, it cannot say what level of risk is acceptable in exchange for expected benefits. Nor can it say whether it is ethically acceptable to force citizens to take risks with their health.

The common profluoridation claim that “all qualified” experts support the safety and effectiveness of fluoridation is simply not credible. Science and scientists are never so unambiguous. The apparent unanimity on fluoridation is based in political processes, not science.

The scientific and political histories of fluoridation are inextricably intertwined. Once fluoridation became explosively controversial, the dispute had profound effects on the subsequent conduct of research and the interpretation of results.

USPHS

The USPHS endorsed fluoridation in 1950 overriding the objections of its own scientific authorities, who considered endorsement premature.

Proponents quickly realised that the public would not accept objective statements on safety assessment – they had to dogmatically state “research has unequivocally proven fluoridation to be safe for everyone” when the reality was that there was little evidence either way. By the mid 1960s research on potential adverse health effects had essentially come to a halt in the USPHS. The emphasis shifted to political promotion.

The USPHS was responsible for both promoting fluoridation and assessing its safety.

Research in countries like India takes an environmental health perspective on possible health risks. Such research could be very useful. But promoters usually try to discredit the work, or dismiss it as “irrelevant to fluoridation”.

Any US research looked only for obvious clinical symptoms; not early warnings. It also excluded key subpopulations at special risk – e.g. kidney patients in the Newburgh study.

Research was funded by promoters, and conducted by converts to the cause. Authors consistently interpreted incomplete data and ambiguous findings as persuasive of the absence of risk. They uniformly rejected every result that suggested potential harm as “clinically insignificant” or “not attributable to fluoride”.

The existing studies (1991) are much less than conclusive of safety claims.
Indian studies have shown clear dose-response curves for skeletal fluorosis over a 50 year period, even at 1 ppm.

Reviews cannot be trusted, as the review bodies, though sounding reputable, are likely pro-fluoridation, and the reviews therefore biased, often heavily. There are exceptions of course – Rose and Marier, Teotia and Teotia.

*While the antifluoridationists are usually portrayed as not scientific, they often act more scientifically in the debate than the profluoridationists.*

*The political profluoridation stance has evolved into a dogmatic, authoritarian, essentially antiscientific posture, one that discourages open debate of scientific issues.*

*The profluoridation lobby has the greatest control over how the debate is conducted, but they seem to have locked themselves in a corner, where change may well bring defeat.*
COMMUNITY WATER FLUORIDATION IN AMERICA: THE UNPRINCIPLED OPPOSITION

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THE UNPRINCIPLED OPPOSITION AND THE TECHNIQUES THEY EMPLOY:

Bernhardt & Sprague compiled a list of techniques fluorophobics frequently use in an attempt to stop the process of fluoridation. A detailed review of these techniques follows. It will become obvious as the list is reviewed why the author and others often refer to these as the techniques of health terrorism:

1. **Neutralizing Politicians:**
   
   - Once fluoridation legislation has been introduced, fluorophobic extremists attempt to convince state & local legislative officials to remain neutral, rather than make the appropriate health policy decision to fluoridate the water supply.
   
   - Antifluoridationists try to convince the legislative officials to refer the issue to public vote rather than to decide the issue through the legislative process. Fluorophobics attempt this because they are much more adept at running a scare campaign focused on the public than they are at convincing skeptical legislators to agree with their views. In those rare instances where fluoridation has been subjected to referendum, only a small percentage of the elections are lost. Moreover, they are not lost because of issues of science, but because of low voter turnout and because of ruthless scare campaigns that are focused on the most emotionally vulnerable citizens.
• These laundry lists are repeated so much in pamphlets, letters-to-the-editor, and phone calls to talk-radio shows, that the public may actually begin to believe the unsubstantiated claims.

• The appearance of an allegation in print (such as in letters to editors) is often believed by the public to be evidence of the allegation's validity. The public incorrectly assumes that the "authorities" (in this case print media editors) would not allow allegations to be printed if they were untrue. Thus, the media often become unwitting pawns of the antifluoridationists, unless the newspapers are large enough and sophisticated enough to have employed qualified and responsible science editors to eliminate from publication those letters that are scientifically unsound and which constitute a potential for harm to the public.

3. The third technique involves the use of **Half-Truths**, where an out-of-context statement is used to imply a cause-and-effect relationship with some evil result alleged to have been caused by fluoridation:

• For example, fluorophobics claim that "Fluoride is poison, so don't let them put it in our water." This statement ignores the principle that toxicity is related to dose of a substance and not to mere exposure to the substance itself. For example, chlorine, Vitamin D, table salt, iodine, antibiotics, even water, serve as excellent examples of substances that are harmful in the wrong amounts but beneficial in the correct amounts.

• Another example is: "Fluoride causes dental fluorosis or mottling." By itself, this claim fails to take into account either the source of the fluoride, the amount of fluoride, the mechanism of fluoride exposure, or the time of exposure as related to the dental age of the person exposed. Community water fluoridation is not responsible for causing dental fluorosis. Limited numbers of the population have an extremely mild form of fluorosis that has been primarily attributed to improper supplementation of fluoride through careless prescriptive practices and the inappropriate ingestion of large amounts of fluoride-containing dentifrice by young children not properly supervised during tooth-brushing.
Another oft-used claim by fluorophobics is that "Insufficient research has been carried out to prove safety, and therefore consumers and government officials are urged to wait until all doubt about safety of fluoridation has been 'scientifically' resolved." This ludicrous argument could be used indefinitely in that it is impossible to ever prove absolute safety for all time for anything. Unqualified acceptance of this argument would mean that literally all technological advancements achieved in the age of science would have to be eliminated. Thousands of studies and untold risk-benefit analyses have shown that fluoridation is safe and effective for the entire population.

5. A fifth technique involves the Quoting of Inaccurate Statements and the Use of Statements Taken Out of Context:

- The best way to illustrate this common fluorophobic technique is to refer to two frequently used antifluoridation publications, the Lifesavers Guide to Fluoridation (a pamphlet) and Fluoride: the Aging Factor, (a monograph). Both use essentially the same "scientific references," both are distributed frequently in campaigns opposing fluoridation, and both documents were marketed by their author as "scientific documents." The one-sheet pamphlet claims over 250 references.

- A group of 20 scientists and public health officials from around the United States decided to actually track down the original references in order to evaluate their validity as used by the author. It took two years and the production of a 184-page textbook to adequately document that this pamphlet was a piece of scientific nonsense. The refutation was appropriately entitled "Abuse of the Scientific Literature in an Antifluoridation Pamphlet." What the group found through its Herculean effort was astonishing:
  
  - Of the 250 references - only 48% were from reputable scientific journals- some of the alleged "scientific studies" were actually references to letters to the editors of newspapers;
  
  - 240 of the 250 citations were incompletely referenced;
Antifluoridationists occasionally find a credentialed individual to speak against mainstream science. The statements by these marginalized individuals, while of questionable authority, are often exploited by the fluorophobics. Unfortunately, a most flagrant abuse of the public trust occasionally occurs when a physician or a dentist, for whatever personal reason, uses their professional standing in the community to argue against fluoridation, a clear violation of professional ethics, the principles of science, and community standards of practice.

Some nationally-known figures whom may have opposed fluoridation early in their professional careers prior to the accumulation of overwhelming scientific evidence in its favor, often have their earlier statements quoted despite having changed their position to one of support for fluoridation.

As an example, the fluorophobics repeatedly claim that Nobel Laureate and physician Hugo Theorell "condemns" fluoridation when, in fact, he publicly changed his position to one of support as far back as 1967.

7. The seventh technique involves the **Conspiracy Gambit**:

- Because alleged conspiracies are difficult to disprove, they are a favorite of the health terrorists.

- The alleged "conspirators" often include the American Medical Association, the American Dental Association, the equipment and chemical supply companies, the Communist Party, both the aluminum and phosphate fertilizer industries, toothpaste manufacturers, or any other organization appearing to be threatening to the antifluoridationists. Highest on their list of conspirators is the "government" (including the Public Health Service, the Environmental Protection Agency, the prestigious National Institutes of Health, the world-renowned Centers for Disease Control, and the Food & Drug Administration).
In media circles, there is a saying that "everyone is the same size on TV." In other words, debates give the illusion that a scientific controversy exists when no credible people support the fluorophobic's view. Public debates promote the illusion that there are equal numbers of "scientists" on each side of the issue. The vision of "dueling PhD's or dueling doctors" encourages the public to reject fluoridation until the "experts on both sides can agree."

An opponent of fluoridation, utilizing the laundry list approach, can present more misinformation in five minutes than can be refuted in five hours, thus fostering confusion on the part of the public. Proponents are never provided enough time to adequately refute the fluorophobics' charges, because complete refutations, by their nature, take much longer than the sound-bite length antifluoridationists' charges. It was previously mentioned how it took two years' effort and a 184-page textbook to refute allegations made in a one-sheet antifluoridation pamphlet.

Public exposure favors the opponents, enabling him or her to gain name recognition for the materials, services, or viewpoint they are promoting. Like parasites, opponents steal undeserved credibility just by sharing the stage with respected scientists who are there to defend fluoridation.

It is impossible to compete against opponents without appearing to discredit them personally. When a proponent is arguing against a health terrorist who is spreading misinformation, the proponent cannot separate the anti-science message from the anti-science messenger. Moreover, the debate format often results in the public's sympathy vote for the obvious underdog, the fluorophobics. Also, since fluorophobics are quick to threaten to file lawsuits even when they have no case, this exposes their detractors to legal harassment by the opponent's attorneys. You can be assured though, that while threats to sue honest scientists are frequently made, few suits have actually been filed, and none have been successfully pursued by antifluoridationists.
SUMMARY AND CONCLUSIONS:

Fortunately, contemporary antifluoridationists' tactics have served more to delay fluoridation rather than stop it, although there are still areas of the country where fluoridation efforts are nonexistent. Unfortunately, antifluoridationists' political efforts significantly increase the costs to society for health care because the delays translate to more dental cavities, more pain, more infection, and higher dental treatment costs. Antifluoridationists' futile efforts also artificially raise costs to taxpayers when: (1) public agencies are forced to repeatedly defend fluoridation to, judges, governors, agency administrators, legislators, and the media (including financing of the tremendous costs of litigation and legislative challenges) and when (2) public agencies are required to spend more to subsidize dental treatment for certain public beneficiaries (e.g., prison inmates, Head Start children, Native Americans, military personnel and their dependents, veterans, senior citizens, the medically indigent, the institutionalized, and others).

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