

REVIEW ARTICLE

Fluorine—A current literature review. An NRC and ATSDR based review of safety standards for exposure to fluorine and fluorides

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Abstract

Background: A review of the literature of the element fluorine and its bonded-form, fluoride, was undertaken. Generally regarded as safe, an expanding body of literature reveals that fluoride's toxicity has been unappreciated, un-scrutinized, and hidden for over 70 years. The context for the literature search and review was an environmental climate-change study, which demonstrated widespread fluoride contamination by smokestack emissions from coal-fired electricity-generating plants. The objective of this review is to educate and inform regarding the ubiquitous presence and harmful nature of this now ever-present corrosive and reactive toxin.

Methods: Methods include examination of national health agency reviews, primarily the National Research Council (NRC), Agency for Toxic Substances & Disease Registry (ATSDR), standard medical toxicology references, text books, as well as reports and documents from both private and public research as well as consumer-based NGOs. Study criteria were chosen for relevancy to the subject of the toxicity of fluoride.

Results: Fluoride is the extreme electron scavenger, the most corrosive of all elements, as well as the most-reactive. Fluoride appears to attack living tissues, via several mechanisms. Fluoride renders strong evidence that it is a non-biological chemical, demonstrating no observed beneficial function or role in organic chemistry, beyond use as a pesticide or insecticide. Fluorine has a strong role to play in industry, having been utilized extensively in metals, plastics, paints, aluminium, steel, and uranium production.

Conclusion: Due to its insatiable appetite for calcium, fluorine and fluorides likely represent a form of chemistry that is incompatible with biological tissues and organ system functions. Based on an analysis of the affects of fluoride demonstrated consistently in the literature, safe levels have not been determined nor standardized. Mounting evidence presents conflicting value to its presence in biological settings and applications. Evidence examined in this review of the literature, and specifically the recent report by the National Research Council (NRC), offer strong support for an immediate reconsideration concerning risk vs benefit. Consensus recommendations from several sources are presented.

Keywords: Fluorine; fluoride; water; teeth; bone; thyroid; depression; pollution; health; non-fever illness; disease vector; poison; chemical; corrosion; hypertension; hip fractures; immune; calcium; osteoporosis; cancer; Alzheimer's; IQ deficits; kidney; stroke; arthritis; heart attack; mitochondrial poisoning

Fluorine physical structure

Fluorine occupies a unique place in nature and in atomic structure. The element fluorine has nine protons in its nucleus. This degree of electronegativity seeks and demands electrons. It is the most reactive of all elements (Chemistry and Physics CRC Handbook; Weast 1989).

Fluorine is a naturally occurring, widely distributed element, and a member of the halogen family, which includes chlorine, bromine, and iodine. However, the elemental form

of fluorine, a pale yellow-green, irritating gas with a sharp odor, is so chemically reactive that it rarely occurs naturally in the elemental state. Fluorine occurs in ionic forms, or combined with other chemicals in minerals like fluorospar, fluorapatite, and cryolite, and other compounds. Fluorine gas reacts with most organic and inorganic substances; with metals it forms fluorides and with water it forms hydrofluoric acid. Fluorine gas is primarily used to make certain chemical compounds, the most important of which is uranium

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hexafluoride, used in separating isotopes of uranium for use in nuclear reactors and nuclear weapons (Chemistry and Physics CRC Handbook; Weast 1989).

Chemistry of fluorine

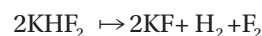
The fluoride ion is basic, therefore hydrofluoric acid is a weak acid in water solution. However, water is not an inert solvent in this case: when less basic solvents such as anhydrous acetic acid are used, hydrofluoric acid is the strongest of the hydrohalogenic acids. Also, owing to the basicity of the fluoride ion, soluble fluorides give basic water solutions. The fluoride ion is a Lewis base, and has a high affinity to certain elements such as calcium and silicon. For example, deprotection of silicon protecting groups is achieved with a fluoride. The fluoride ion is poisonous.

Fluorine can replace hydrogen wherever it is found. The substitution of fluorine for hydrogen in organic compounds offers a very large number of compounds. An estimated fifth of pharmaceutical compounds and 30% of agrochemical compounds contain fluorine. The $-CF_3$ and $-OCF_3$ moieties provide further variation, and more recently the $-SF_5$ group (Chemistry and Physics CRC Handbook; Weast 1989). Dreisbach (1966, p. 189) states: 'Fluorine and fluorides act as direct cellular poisons by interfering with calcium metabolism and enzyme mechanisms'. Fluorides form an insoluble precipitate with calcium and lower plasma calcium. Hydrogen fluoride (hydrofluoric acid) is directly corrosive to tissues. Neutral fluorides in 1–2% concentrations will cause inflammation and necrosis of mucous membranes (NRC 2006).

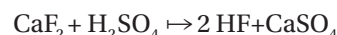
Fluorine's reactivity makes it excellent for reacting with and breaking down other compounds. The microelectronics industry uses fluorine to etch circuit patterns onto silicon and tungsten. Nitrogen trifluoride breakdown powers this process.

Production of fluorine

Industrial production of fluorine entails the electrolysis of hydrogen fluoride in the presence of potassium fluoride. This method is based on the pioneering studies by Moissan (see below). Fluorine gas forms at the anode, and hydrogen gas at the cathode. Under these conditions, the potassium fluoride (KF) converts to potassium bifluoride (KHF_2), which is the actual electrolyte. This potassium bifluoride aids electrolysis by greatly increasing the electrical conductivity of the solution.



The HF required for the electrolysis is obtained as a byproduct of the production of phosphoric acid. Phosphate-containing minerals contain significant amounts of calcium fluorides, such as fluorite. Upon treatment with sulfuric acid, these minerals release hydrogen fluoride:



History

The mineral fluorspar (also called fluorite), consisting mainly of calcium fluoride, was described in 1530 by Georgius Agricola for its use as a flux. Fluxes are used to promote the fusion of metals or minerals. The etymology of the element's name reflects its history: Fluorine is from Latin: *fluere*, meaning 'to flow'.

In 1670, Schwanhard found that glass was etched when it was exposed to fluorspar that had been treated with acid. Carl Wilhelm Scheele and many later researchers, including Humphry Davy, Caroline Menard, Gay-Lussac, Antoine Lavoisier, and Louis Thenard, all would experiment with hydrofluoric acid, easily obtained by treating fluorite with concentrated sulfuric acid.

Owing to its extreme reactivity, elemental fluorine was not isolated until many years after the characterization of fluorite. Progress in isolating elemental fluorine was slowed because it could only be prepared electrolytically and even then under stringent conditions since the gas attacks many materials. In 1886, the isolation of elemental fluorine was reported by Henri Moissan after almost 74 years of effort by other chemists. The generation of elemental fluorine from hydrofluoric acid is exceptionally dangerous, killing or blinding several scientists who attempted early experiments on this halogen. These individuals came to be referred to as 'fluorine martyrs'. For Moissan, it earned him the 1906 Nobel Prize in chemistry.

The first large-scale production of fluorine was undertaken in support of the Manhattan project, where the compound uranium hexafluoride (UF_6) had been selected as the form of uranium that would allow separation of its ^{235}U and ^{238}U isotopes. Today both the gaseous diffusion process and the gas centrifuge process use gaseous UF_6 to produce enriched uranium for nuclear power applications. In the Manhattan Project, it was found that UF_6 decomposed into UF_4 and F_2 (ATSDR 2003).

Earliest toxicology research citations

The fluoridation of the public water supply began after World War II.

The origins of the national program to add fluoride to the public water supply are discussed in several scientific reports (Bryson 2004). The points of contention raised in these earlier references are still standing. Sixty-five years ago, the practice of fluoridation began in two test locations. Controversy surrounded the project as there were too many questions that had not been asked or answered—or had the amount of time necessary to be answered. Yet, without any answers, the program expanded. The fact that these questions remain unanswered, a fact that the reader will encounter in this report, is a fact that raises more questions. Prevention of dental caries is the sole reason given for the addition of this toxic electron-scavenging halogen into public water. Once there, its effects are unavoidable. If this dental-carries-reduction benefit is not accomplished, if the addition of fluoride to the water does not lower the

incidence of dental caries in all who drink it, then there is no justification for its presence. It is demonstrated by the UN Health report (see WHO-DMFT) that dental caries declined worldwide regardless of fluoridation. Upon learning that fluoride is ineffective as a decay-preventive, then the program of adding fluoride to the public water supply 'de-constructs'. If it remains, it must give another reason for its existence at the tax-payers expense. What will be the new reason for keeping fluoride in the water? A constitutional argument could be made as well, that no one has the right to poison public water—especially the government. A voice of sanity and reason is heard in these words of warning about the dangers that could result from not waiting to hear the answers when questions have been raised.

Fluoridation of Water
Congressional Record
3/24/1952

I wish to discuss, briefly, the pros and cons of adding fluorine to the communal water supply, in an effort to prevent dental caries in children. This subject is of a great deal of interest to all of the country.

The Special Committee on Chemicals in Food has just completed exhaustive hearings, the first of its kind, upon the question of adding fluorine to the water supply. We had before the committee 18 witnesses who qualified as experts on the subject. There certainly was no unanimity of opinion among these experts. This was true because the scientists felt that certain experiments now in progress were not far enough along in order for them to issue a sound opinion.

Mr Speaker, a year ago (1951) I introduced a bill which would permit the Commissioners of the District of Columbia to add fluorides to the public water supply of Washington, DC. I did this because I thought the adding of fluorides at that time was a good thing, and I wanted to have some discussion upon the subject. The Commissioners did not wait for a hearing on the bill; and without legislative authority, and under the prodding from the Health Department, they appeared before the Appropriations Committee requesting moneys to put the plan into operation.

I note in the Sunday Star of Sunday, March 23, 1952, that—'Nearby Maryland is being tested for fluoride effects, and that the United States Public Health Service is now making a long range study of its value in water.'

'The Public Health Service is trying to find out exactly how fluorides fight tooth decay and how it reacts in some parts of the body.'

I think it is all to the good, Mr Speaker, that the Public Health Service will continue to investigate as to what happens when fluorides get into the system of the individual who is ill.

I can say to my colleagues, quite frankly, that until I had the advantage of hearing all of the experts on this question, I thought that fluorine added to the water supply might be beneficial to every one. I was misled by the Public Health Service. I am a former State health director and have always

supported the Public Health Service in the measures that they have advocated. I am sorely disappointed that they now are advocating every single soul in the community should take fluorine before all the facts of the experiments now in progress have been completed. It may be a good thing for everyone, but we ought to know whether sick children or adults with kidney disease, diabetes, fracture of a bone, or thyroid disturbances or tuberculosis, or any chronic disease, are able to eliminate fluorides as effectively as normal people do. In the testimony before our committee I could find no record of any such studies.

I am further disturbed, Mr Speaker, because I was misled and perhaps others have been misled by statements that the American Medical Association had given their unqualified approval of this plan. Let me call your attention to what Dr George Lull, secretary and general manager of the AMA, said in an insert in the record of the hearings on March 6, 1952, which appears on pages 3971 and 3972 of the printed hearings, and I quote:

'The council purposely refrains from making any recommendations that communities support or oppose projects for the fluoridation of water supplies.'

On page 3972:

'The house of delegates did not urge or recommend that any community undertake to fluoridate their water supplies.'

Mr Speaker, that statement is of a definitive nature. I was led to believe that they had given fluoridation of the water their wholehearted support. I was told this by the Public Health Service. I have been guilty of quoting the American Medical Association as giving mass fluoridation their unqualified approval.

Mr Speaker, despite my best efforts, and from the evidence before my committee, I cannot find any public evidence that gave me the impression that the American Medical Association, the Dental Association, or several other health agencies, now recommending the fluoridation of water, had done any original work of their own. These groups were simply endorsing each other's opinions.

The possibility of using fluorides for control of children's dental caries is an attractive one and in my opinion warrants additional study. There is no scientific basis for recommending immediate acceptance of the proposals to treat the entire population with fluorides. The mass medication of fluorides is still in the experimental category, and there is certainly a need for additional scientific studies. There is nothing that presents an urgent decision until decisive experiments have been done. It will then be time to make the decision.

It is quite possible that the use of fluorides in preventing dental caries will be a major discovery in the field of dentistry. It is too early to evaluate the results of experiments now in progress.

Mr Speaker, it is disturbing to me when the men in the Public Health Service, who, as late as 1950, were not ready to endorse the universal use of fluorine have now, almost to a man, come out for the endorsement. I want to refer to

some published papers of Dr Francis A. Arnold, National Institute of Health. The papers published in 1948, 1949, and 1950 said in substance:

'The evaluation of the effects of fluorine in water has not been established and must await until the experiments now in progress are completed.'

Dr Arnold published another paper on dental research in May of 1951. The paper appeared in Tufts College dental school magazine. The paper refers to dental research as well as to the use of fluorine in water. I quote from page 3778 of (these) hearings held March 17, 1952:

'It is too early to evaluate the effects of this increased research activity on the improvement of the dental health of the children in the United States.'

'Fluoride Therapy for the Control of Dental Caries' by Dr Arnold, reprinted in the Journal of the American Dental Association in October 1948 states:

'At the present there is no acceptable controlled scientific evidence in an adequate number of observations with which to evaluate the supplemental feeding or fluoridation for caries control.'

It seems unthinkable to me that we should proceed with universal medication until these facts have been carefully examined.

Mr Speaker, at Newburg, NY, an exhaustive experiment is being carried of which will be completed in about 5 years. [Begun in 1947] When completed they will have some conclusive evidence as to the effect, if any, fluorine might have on the health of the older group and those with chronic diseases. This will also include the effects upon the unborn child. Dr David B. Ast, of the American Public Health Service, is heading up this experiment. He published an article in volume 4, No. 6, of the June 9, 1950 issue of the *American Journal of Public Health* on the question of fluorides in the water. A final conclusion of the article appears on page 4042 of the hearings, and I quote:

'Final conclusions regarding the possible systemic effects of fluoride on the dosage employed should not be drawn before the termination of the 10-year study. More refined techniques may also be available in the future in studying pertinent aspects of the problem. It must be emphasized, however, that a longer period of observation is required before final conclusions can be drawn. The possibility of demonstrated accumulative affects of the fluorides in the final years of the 10-year study cannot be eliminated at this time.'

Mr Speaker, I repeatedly asked the following question of nearly every witness which appeared before our committee:

'What experiments have been carried on to demonstrate the effects of fluorides might have upon older people and those with chronic diseases, or in abnormal children?'

All of the advocates of the use of fluorides in the water said that no conclusions had been reached, but that studies were in progress. Again, I repeat, Mr Speaker since these studies are in progress, it seems to me to be in the public interest for communities that wish to use fluorides in their

water supply to know that the results of experiments now being made have not been completed or published.

Mr Speaker, every member of Congress probably sends out numerous year-books of the Department of Agriculture. The 1950-1951 yearbook has a chapter entitled 'Hazards and Potential Drugs.' On page 722, this statement is found:

'For example, the work of the pharmacology laboratory demonstrated that the fluoride ion inhibits the bone enzyme phosphatase in young rats and thereby retards calcification of the leg bones.'

The Department of Agriculture has recommended that no fluorides be fed to brood sows. Experimental work on rats and mice indicate a lessened mental reaction in rats and mice who have had fluorides. What effect fluorides might have on the unborn child has not been established. Evidence points to the fact that the placenta carries a large amount of fluorides.

A check of the vital statistics of Grand Rapids, Michigan—which is the only city of any size that has had artificial fluoridation for more than 4 years—shows that the death rate from heart disease in the year 1944 numbered 585. Four years later, after fluoridation had started, there were 1059 deaths. There was an increase of 50% in the deaths from nephritis. There was an increase of 50%, over a period of 4 years, in the deaths from intra-cranial lesions. These are official figures contained in the Vital Statistics of the United States published annually by the United States Public Health Service. I am not saying that fluoridation was the cause. However, the Public Health Service takes pride in pointing out, through statistics, that health might even be better when fluorides are in the water. Public records provide no support for their conjectures.

I have also noted, Mr Speaker, that the District of Columbia Commissioners propose to use sodium silicofluorides. This is cheaper, but the most dangerous type of element. It forms a highly toxic fluoric acid. If fluorides must be used, the biochemists recommend that sodium fluoride should be used.

This is not an urgent matter. I would recommend the go-slow sign until we are thoroughly convinced that no damage will come to the sick child, or to the individuals in the old age group, who may have chronic diseases. The picture today is not clear. Communities who insist on putting fluorides in their water should know that experiments now in progress, which will be completed in 6 years, may supply the answer as to whether universal medication of water will be a good thing for all the people (A.L. Miller 1952. United States Congress Report).

Other early medical/dental opinions on fluoride

Practicing doctors and dentists voiced their concerns, beginning at the turn of the 1900s, about the adulteration of the food supply. Many protested the bleaching of flour, the use of manufactured sugar, and the growing deception that man could make the same food with his chemistry set that the earth produced with its solar-powered system of photosynthesis. Dr

Lee and others advocated that there is an organic process in food production, whereby minerals require a transformation by living cells, microbes, fungi, and bacteria in the soil of the earth before they can be utilized by other life forms. If fluoride was going to be of any use to the animal kingdom, stated Dr Lee, then it must first be transformed in a similar process to element cobalt for example (Lee 1953).

It is probable that fluoride as a food is only that kind of fluoride that has entered in an organic combination by passing through plant life before we make use of it. Inorganic fluorine is a cumulative poison, which means that it accumulates in the body even if taken in very small doses. Organic fluorine does NOT accumulate in the body, regardless of the dosage, and is unquestionably far more effective in preventing dental decay. Whole wheat grown in Deaf Smith County, Texas, contains up to 700 ppm of fluorine (calcium) but never has caused fluorosis, while inorganic fluorine (sodium and silico-) in drinking water may cause such fluorosis even in amounts as small as 0.9 ppm (Lee 1953).

Inorganic cobalt is poisonous to the human system, and it cannot be used in any way until converted by soil microbes into B12. Fluorine probably is worse at being a cumulative poison, as it accumulates in the bones and makes them more and more brittle if taken as the inorganic form. There is no known antidote for this process (Lee 1953).

So the dangers of the reckless use of fluorine seem too obvious to permit the wholesale addition of this element to drinking water before the test installations are completely reported on. A 10-year period was stated to be essential before any reliable statistics were to be available. That was when the first fluoridation was begun back in 1947. Why this haste at the present moment? Who is pushing this dangerous procedure, and why? (Lee 1953).

(water fluoridation) is saddling the use of fluorides in poisonous forms to make us believe that we are preventing tooth decay. Maybe it will; no doubt the intestinal flora of the child will in some degree convert the inorganic fluoride into organic. But what about the greater part that is NOT converted, that part which remains in the bone tissues, and renders the bones brittle, and acts to poison glandular cells? For the sake of safety, we should not take into our food regime ANY INORGANIC FLUORINE AT ALL (Lee 1952, p. 145).

Adverse effects of sodium fluoride

Acne, nausea, vomiting, anorexia, diarrhea, mild-bleeding, pain around the joints, discolored nails and teeth (mottled enamel). These effects are associated with sodium fluoride levels between 3–5 mg/kg and more (Poisindex 2006).

Sodium fluoride can be a direct cellular toxin

At appropriate concentrations, sodium fluoride can be a direct cellular toxin which interferes with calcium metabolism and enzyme mechanisms by activating both proteolytic and glycolytic functions. Fluoride ions induce an efflux of potassium from red blood cells. Hyperkalemia has been implicated

in contributing to fluoride-induced dysrhythmias, along with hypocalcemia (Drugdex 2006; NRC 2006).

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumors. This cohort was also subject to multiple concurrent toxins and aluminum in particular. In vitro studies of sodium fluoride in high concentrations exposed to human keratinocytes caused abnormal DNA synthesis (DrugDex 2006). Sodium fluoride is an IARC group 3 chemical that has not been classified as to carcinogenicity in humans (Poisindex 2006).

Fluoride levels found in drinking water are not expected to increase the risk of adverse pregnancy outcome. In experimental animals, fluoride toxicity in the mother is associated with adverse pregnancy outcome. Human pregnancy exposure to drinking water with 12–18-times the recommended fluoride concentration has been reported to be associated with impaired development of the infant's deciduous (baby) teeth (Reprotox 2004).

Fluoride is secreted in human milk in small quantities and the breastfed infant will receive between 5–10 µg fluoride/day. In contrast, the bottle-fed infant whose formula is prepared with fluoride supplemented drinking water will ingest between 160–800 µg/day (Reprotox 2004).

NIOSH has published a TLV of 2.5 mg/m³ for sodium fluoride (Poisindex 2006). This value is also published as an OSHA PEL and an ACGIH TWA (HSDB 2005). The IDLH, Immediately Dangerous to Life and Health, is 250 mg/m³ (HSDB 2005).

Clinical data

The minimum daily recommended dietary levels for adult oral dose of sodium fluoride is 4 mg sodium fluoride per day for males and 3 mg/day for females with a tolerable upper intake level of 10 mg/day. Treatment regimens for osteoporosis, a non-labeled indication, typically are in the dose range of 33–220 mg sodium fluoride daily (Poisindex 2006).

In acute poisoning, sodium fluoride taken by mouth is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastro-intestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcemia, hypomagnesemia, hyperkalemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Although there is much inter-individual variation, a single oral dose of 5–10 g of sodium fluoride would be lethal within 2–4 hours in an untreated adult (Martindale 2006).

Chemistry and pharmacokinetics of fluoride (NRC report)

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 US Environmental Protection

Agency (EPA) maximum contaminant-level goal (MCLG), including the accumulation of fluoride in bone, pharmacokinetic modeling, cross-species extrapolation, and susceptible populations.

Chemistry, units, and measurement

Fluoride is the ionic form of fluorine, the most electronegative element. Water in the US is typically fluoridated with fluoro-silicates or sodium fluoride. In water at approximately neutral pH, fluorosilicates appear to entirely dissociate, producing fluoride ion, hydrofluoric acid (HF), and silicic acid ($\text{Si}(\text{OH})_4$). Fluoride reversibly forms HF in water. It also complexes with aluminum.

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 later in this chapter. A number of different units are commonly used to measure fluoride concentrations in water and biological samples (Table 1). Because the atomic weight of fluorine is 19, 1 $\mu\text{mol/L}$ is equal to 0.019 milligrams per liter (mg/L). Bone ash is typically ~ 56% of wet bone by weight (Rao et al. 1995), so 1000 milligrams per kilogram (mg/kg) of fluoride in bone ash is equivalent to ~ 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 ~ 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 over-predict 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).

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, ~ 99%, is contained in bone.

Fluoride is well absorbed in the alimentary tract, typically 70–90%. 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 can increase the uptake of aluminum into bone (Ahn et al. 1995) and brain (Varner et al. 1998).

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 40–90% 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 ~ 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; Inkiewicz and Krechniak 2004). Mullenix et al. (1995) reported atypically high, dose-dependent T/P ratios for the rat brain: more than 20 for control animals and ~ 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). Experimental work in growing dogs demonstrates that extrarenal clearance, almost entirely

Table 1. Commonly used units for measuring fluoride.

Medium	Unit	Equivalent
Water	1 ppm	1 mg/L
Plasma	1 $\mu\text{mol/L}$	0.019 mg/L
Bone ash	1 ppm	1 mg/kg

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 by the gut 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 ~ 30 min. 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 ~ 6400 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. Twenty years might not represent a true half-life. Recent pharmacokinetic models (see below) are non-linear, suggesting that elimination rates might be concentration-dependent. 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 non-linear 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 ~ 10,000 mg/kg; above that concentration the curve levels off. (Based on the chemical structure of fluorapatite, $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$, 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 ~ 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 in bone vs water

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 26–90, 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.

A table in this reference summarizes data on fluoride content of the iliac crest, the bone modeled by Turner et al. (1993) and Rao et al. (1995). Zipkin et al. (1958) concluded that average bone fluoride concentrations were linearly related to water concentration. The committee regressed individual-level bone concentrations vs water concentrations (a group measure of exposure) and individual-level covariates such as age. (This analysis is partially ecologic.) A figure in this reference plots bone vs water concentrations and the result of simple regression with no covariates. (Note the apparent heteroscedasticity.) The model was improved by including residence years and sex; age had little additional impact and was omitted in the final model.

Several cross-sectional studies have found an association between fluoride bone concentrations and age (Jackson and Weidman 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 Weidman (1958) were unusual in finding a leveling off at an older age. However, most studies did not have information on length of exposure, a variable often correlated with age ($R=0.41$ in the Zipkin et al. 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 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. 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 ~ 8100 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. (1958) 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 under-predict. Only the model of Rao et al. (1995) was constructed to examine lifetime exposure. Assuming 70 years of exposure at 4 mg/L in water, Rao et al. predicted fluoride concentrations of 10,000–12,000 mg/kg in bone ash for females. Even 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 5-fold because of the non-linear kinetics. Unfortunately, Rao et al. did not publish predictions for 2 mg/L. The regression model predicts ~ 5000 mg/kg ash for females after 70 years of exposure. This value exceeds the mean value (4500 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 under-estimate 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 ~ 5700 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 Weidman 1958; see Turner et al. 1993 for unit conversions). In an area of rural Finland where fluoride in drinking water exceeding 1.5 mg/L, the average bone concentrations from 57 autopsies were 3490 mg/kg ash in females and 2830 mg/kg ash in males (Arnala et al. 1986). Most had lived their whole lives in the same place, most were over 50, and seven had impaired renal function. For 16, fluoride concentrations were measured in the water sources (2.6 ± 1.4 mg/L); bone concentrations were 4910 ± 2250 mg/kg ash. In a later study of the same area of Finland, the mean bone concentration in 18 hip fracture patients was 3720 ± 2390 mg/kg, assumed to be ash (Arnala et al. 1986). The mean age was 79, 14 were female, three had diabetes, and one 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 4000–5000 mg/kg ash. Considerable variation around the average is expected.

Fluoride uptake measured in bones

A number of clinical studies measured bone fluoride concentrations after therapeutic treatment (van Kesteren et al. 1982; Bayley et al. 1990; Gutteridge et al. 1990; Orcel et al. 1990; Sogaard et al. 1994; Lundy et al. 1995). A figure in the reference summarizes these data, plotting fluoride concentrations in bone ash after treatment vs total exposure from the studies. The weighted least squares (WLS) regression line weighted points according to the number of participants in each trial. 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 (Turner et al. 1993). This analysis is ecologic, plotting average bone concentrations vs 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 non-linear, we would not necessarily expect people with the same cumulative exposure to have the same bone fluoride concentrations. Indeed, the model may over-predict bone concentrations for long-term exposure to lower fluoride concentrations via water. A figure 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 et al.'s (1993) pharmacokinetic model suggests that short-term (months-to-years), high-dose exposures 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.

Ofrats, mice, and men

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 extra-renal 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 ~ 5-times larger than humans to reach the same plasma concentration (Dunipace et al. 1995).

For evaluating bone studies, Turner et al. (1992, p. 587) estimated that 'humans incorporate fluoride greater than 18-times more readily than rats when the rats are on a normal calcium diet'. This comparison was also based on water concentrations.

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 (NRC 2006).

Organofluorides

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; $C_8F_{17}SO_3^-$) and perfluorooctanoate (PFOA; $C_7F_{15}COO^-$).

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, $C_8F_{17}SO_2F$) is used as a starting material for manufacturing polymers and surfactants. Residual POSF in products 'may degrade or metabolize, to an undeterminate degree' to PFOS (Olsen et al. 2004, p. 1600). Certain anesthetics release fluoride ion during use.

Complicating factors

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 cystalites 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 ~ 20% of normal, as measured via creatinine clearance or serum creatinine concentrations (Hanhijarvi 1975; Parsons et al. 1975; Schiffel and Binswanger 1980; Waterhouse et al. 1980; Hanhijarvi and Penttila 1981). Kuo and Stamm (1974) found no association. However, elevated serum concentrations were found in renal patients with normal serum creatinine (Hanhijarvi et al. 1981).

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 ~ 5500–11,000 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. (1986) 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. 1996; 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). Hanhijarvi and Penttila (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 concentrations between men and women (e.g. Torra et al. 1998), others found greater rates of increase with age in females (Husdan et al. 1976; Hanhijarvi et al. 1981). Enhanced release of fluoride in post-menopausal 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. 1986; 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 2-fold. 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 10,000–12,000 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 4000–5000 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.

NRC recommendations for pharmacokinetics research

- 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 non-invasive means of measuring bone fluoride. As discussed in other chapters of this report, some soft tissue effects may be associated with fluoride exposure. Most measurements 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, post-menopausal 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.

Exposure to fluoride

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.

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 (1993) previous 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 (NRC 2006).

Highly exposed sub-populations 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 sub-populations 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 ~ 3–4 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 (NRC 2006).

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 (NRC 2006).

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, ~ 10% on average, among children in US 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 (NRC 2006).

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 sub-groups that are prone to accumulate fluoride into their bones (e.g. people with renal disease). However, three 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 (NRC 2006).

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 (NRC 2006).

The committee's conclusions regarding the potential for adverse effects from fluoride at 2–4 mg/L in drinking water do not address the lower exposures commonly experienced by most US citizens. Fluoridation is widely practiced in the US to protect against the development of dental caries; fluoride is added to public water supplies at 0.7–1.2 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 (NRC 2006).

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 US Public Health Service, and different

considerations were factored into how those guidelines were established (NRC 2006).

Natural source

Fluoride occurs naturally in public water systems as a result of run-off 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 run-off into water. Of the ~ 10 million people with naturally fluoridated public water supplies in 1992, ~ 6.7 million had fluoride concentrations less than or equal to 1.2 mg/L. Approximately 1.4 million had natural fluoride concentrations between 1.3–1.9 mg/L, 1.4 million had between 2.0–3.9 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) (NRC 2006).

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 US for the prevention of dental caries has been set at 0.7–1.2 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). 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 (2002) estimates that ~ 162 million people (65.8% of the population served by public water systems) received optimally fluoridated water in 2000 (NRC 2006).

The practice of fluoridating water supplies has been the subject of controversy since it began (see reviews by Nesin 1956; 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 anti-caries benefit of fluoride is topical and not systemic (Zero et al. 1992; Rolla and Ekstrand 1996; Featherstone 1999; Limeback 1999; 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.

Varying intake levels

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 200–300 mL/h to 2000 mL/h 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).

Daily fluoride consumption

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). 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.

Heilman et al. (1997) found 0.01–8.38 µg of fluoride per gram 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 0.01–0.63 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 (~60 g) of chicken daily at 8 µg of fluoride per g would have an intake of ~0.48 mg (Heilman et al. 1997).

The US Army's policy on fluid replacement for warm-weather training calls for 0.5–1 quart/h (0.47–0.95 L/h), 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/h (1.4 L/h) 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 (US Army 1983). Hourly intake can range from 0.21–0.65 L depending on the temperature (McNall and Schlegel 1968), and daily intake among physically active individuals can range from 6–11 L (US Army 1983, cited by EPA 1997). Non-military outdoor workers in hot or dry climates probably would have similar needs.

Water intakes for pregnant and lactating women are listed separately in the reference. Total water intake for pregnant women does not differ greatly from that for all adult females, 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; Belchetz and Hammond 2003). People with untreated or poorly controlled diabetes mellitus would be expected to have substantially higher fluid intakes than non-diabetic members of the population. The American Diabetes Association (2004) estimates that 18.2 million people in the US (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 16–20 million people in the US, with up to 50% undiagnosed (Brownlee et al. 2002).

Diabetes insipidus, or polyuria, is defined as passage of large volumes of urine, in excess of ~2 L/m²/day (~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). Diabetes insipidus includes several types of disease distinguished by cause, including both familial and acquired disorders (Baylis and Cheetham 1998). Water is considered a therapeutic agent for diabetes insipidus (Beers and Berkow 1999); in addition, some kinds of diabetes insipidus can be treated by addressing an underlying cause or by administering vasopressin (anti-diuretic 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 US at between 40,000–80,000. 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. 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 20–40% 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). Two of the papers described cases of enamel fluorosis in the US 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 US '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 ~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 or 1 mg/L, and severe enamel fluorosis with skeletal fluorosis has been reported with fluoride at 3.4 mg/L. Greenberg, in the NRC (2006) report, recommended that children with any disorder that gives rise to polydipsia and polyuria be supplied a portion of their water from a non-fluoridated source. Table 3 provides examples of fluoride intake by members of several population sub-groups 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, so that some individuals could consume up to 1.7-times as much as others for the same water intake (1.2 vs 0.7 mg/L) (NRC 2006).

Milk is protective against fluoride

Measured fluoride in samples of human breast milk is very low. Dabeka (in NRC 2006) found detectable concentrations in only 92 of 210 samples (44%) obtained in Canada, with fluoride ranging from <0.004–0.097 mg/L. The mean concentration in milk from mothers in fluoridated communities (1 mg/L in the water) was 0.0098 mg/L; in non-fluoridated communities, the mean was 0.0044 mg/L. Fluoride

Table 2. Case reports of fluorosis in association with diabetes insipidus or polydipsia.

Study subjects	Exposure conditions	Comments	Reference
(a) 18-year-old boy, 57.4 kg	(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)	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	Juncos and Donadio 1972
(b) 17-year-old girl, 45.65 kg (United States)	(b) "high" intake of water containing fluoride at 1.7 mg/L since infancy; current intake, 4 L/day (0.15 mg/kg/day)		
2 boys (ages 10 and 11) with familial nephrogenic diabetes insipidus (United States)	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)	Enamel fluorosis; fluoride concentrations in deciduous teeth (enamel layer 50-100 pm from surface) 3-6 times those in controls (normal boys aged 10-14 residing in an area with fluoride at 1 mg/L)	Greenberg et al. 1974
Mother and four children with familial pituitary diabetes insipidus (Israel)	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	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	Klein 1975
Six cases of familial pituitary diabetes insipidus (Australia)	Children had average water intake of 8-10 L/day; two of the children lived in fluoridated areas (1 mg/L)	Moderate (one child) or severe (one child) enamel fluorosis in the two children who lived in fluoridated areas	Seow and Thomsett 1994
Two brothers with pituitary diabetes insipidus (ages 17 and 7) (India)	Well water with fluoride at 3.4 mg/L	Severe enamel fluorosis, skeletal deformities, and radiological evidence of skeletal fluorosis	Mehta et al. 1998

Table 3. Examples of fluoride intake from drinking water by members of selected population subgroups living in fluoridated areas^a.

Population Subgroup (Weight)	Typical consumers ^b				High consumers ^c			
	Water consumption		Fluoride intake ^d		Water consumption		Fluoride intake ^d	
	mL/day	mL/kg/day	mg/day	mg/kg/day	mL/day	mL/kg/day	mg/day	mg/kg/day
Athletes, workers, military (50 kg)	2,500	50	1.8-3.0	0.035-0.06	3,500	70	2.5-4.2	0.049-0.084
Athletes, workers, military (70 kg)	3,500	50	2.5-4.2	0.035-0.06	4,900	70	3.4-5.9	0.049-0.084
Athletes, workers, military (100 kg)	5,000	50	3.5-6.0	0.035-0.06	7,000	70	4.9-8.4	0.049-0.084
Athletes and workers (120 kg)	6,000	50	4.2-7.2	0.035-0.06	8,400	70	5.9-10	0.049-0.084
DM patients (20 kg)	1,000	50	0.7-1.2	0.035-0.06	2,000	100	1.4-2.4	0.07-0.12
DM patients (70 kg)	3,500	50	2.5-4.2	0.035-0.06	4,900	70	3.4-5.9	0.049-0.084
NDI patients (20 kg)	1,000	50	0.7-1.2	0.035-0.06	3,000	150	2.1-3.6	0.11-0.18
NDI patients (70 kg)	3,500	50	2.5-4.2	0.035-0.06	10,500	150	7.4-13	0.11-0.18

^aAssumes all drinking water is from fluoridated community (municipal) sources.

^bBased on a typical consumption rate for the population subgroup.

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

^dBased on fluoride concentrations of 0.7-1.2 mg/L.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.

concentrations were correlated with the presence of fluoride in the mother's drinking water (NRC 2006).

Spak (in NRC 2006) reported mean fluoride concentrations in colostrum of 0.0053 mg/L (0.28 μ M/L) in an area in Sweden with fluoride at 0.2 mg/L in drinking water and 0.0068 mg/L (0.36 μ M/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 μ M/L). No statistically significant difference in milk fluoride concentration between the two areas was found (NRC 2006).

Hossny (in NRC 2006) reported fluoride concentrations in breast milk of 60 mothers in Cairo, Egypt, ranging from 0.002-0.01 mg/L [0.1-0.6 μ M/L; median, 0.0032 mg/L (0.17 μ M/L); mean, 0.0046 mg/L (0.24 μ M/L)]. Cairo is considered

non-fluoridated, with a reported water fluoride concentration of 0.3 mg/L (Hossny et al. 2003). Opinya (in NRC 2006) 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 (NRC 2006).

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 0.007–0.068 mg/L (average, 0.03 mg/L) (in NRC 2006). 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 US 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 drinking water. Fomon et al. (2000) have recommended using low-fluoride water to dilute infant formulas (NRC 2006).

Heilman et al. (1997) found 0.01–8.38 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 0.01–0.63 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 (~ 60 g) of chicken daily at 8 µg of fluoride per g would have an intake of ~ 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 (NRC 2006). 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 170–878 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 the Sichuan Province of China ranged from 49–105 mg/kg dry weight for green teas and 590–708 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 US, 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 US (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 US (Houston area), with a slightly lower mean for decaffeinated (0.14 mg/L) than for caffeinated (0.17 mg/L) coffee. Instant 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 0.15–6.80 mg/L in a variety of juices originating from a number of locations in the US.

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 0.02–1.28 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 2–3-year-old children and 0.60 mg/day for 7–10-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 970–1240 mL, and daily beverage consumption ranged from 585–756 mL.

Burgstahler and Robinson (1997) reported fluoride contents of 0.23–2.80 mg/L in California wines, with seven 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 (Na_3AlF_6) as a pesticide in the vineyards. Martinez (in NRC 2006) reported fluoride concentrations from 0.03–0.68 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 threshold 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 Martinez et al. 1998). Warnakulasuriya et al. (2002) reported mean fluoride concentrations of 0.08–0.71 mg/L in beers available in Great Britain; one Irish beer contained fluoride at 1.12 mg/L.

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 non-cooked, non-reconstituted 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 significantly 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 various 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 40–64-year-old males. Over all ages and both sexes, the estimated average dietary intake of fluoride was 1.76 mg/day; the food category contributing most to the estimated intake was beverages (80%).

Rojas-Sanchez (in NRC 2006) 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 4). 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.

Dental exposure

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 aged 2–16 years surveyed in 1983 or 1986 used fluoride toothpaste (Wagener et al. 1992). Of these children, as many as 15–20% 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 US contains fluoride (Newbrun 1992), usually 1000–1100 parts per million (ppm) (0.1–0.11%), equivalent 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 ($\text{Na}_2\text{PO}_3\text{F}$), or 0.15% w/v fluoride (1.5 mg fluoride ion per cubic centimeter of toothpaste).

Table 4. summary of typical fluoride concentrations of selected food and beverages in the United States.

Source	Range, mg/L	Range, mg/kg
Human breast milk		
Fluoridated area (1 mg/L)	0.007–0.01	—
Nonfluoridated area	0.004	—
Cow's milk	<0.07	—
Soy milk	0.5	—
Milk-based infant formula ^a	<0.2	—
Soy-based infant formula ^a	0.2–0.3	—
Infant food—chicken	—	1–8
Infant food—other	—	0.01–0.7
Tea ^a	0.3–5	—
Herbal tea ^a	0.02–0.15	—
Coffee ^a	0.1–0.6	—
Grape juice ^a	<3	—
Other juices and juice drinks ^a	<1.5	—
Grapes	—	0.8–5
Carbonated beverages	0.02–1.3	—
Wine	0.2–3	—
Beer	0.08–1	—

^aNot including contribution from local tap water.

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 (1991) reported estimates of 0.12–0.38 mg of fluoride ingested per brushing. Burt (1994) and Newbrun (1992) reported estimates of 0.27 mg/day for a pre-school child brushing twice daily with standard-strength (1000 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 0.2–5 g, with means ~ 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 0.42–0.58 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 5; 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 children’s toothpaste, discouraging the use of fluoride toothpaste by children less than 2 years old, avoiding flavored children’s toothpastes, encouraging the use of very small amounts of toothpaste, encouraging rinsing and expectorating (rather than swallowing) after brushing, and recommending careful parental supervision (e.g. Szpunar and Burt 1990; Levy and Zarei-M 1991; Simard et al. 1991; Burt 1992; Levy et al. 1992; 1993; 1997; 2000; Naccache et al. 1992; Newbrun 1992; Levy 1993; 1994; Bentley et al. 1999; Rojas-Sanchez et al.

1999; Warren and Warren and Levy 1999; Fomon et al. 2000). 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 1556 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. Sjogren (2004) 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 0.25–1.0 mg of

Table 5. Estimated typical fluoride intakes from toothpaste.^a

Age group, years	Fluoride intake, mg/day	Age group, years	Fluoride intake, mg/day
Infants < 0.5 ^b	0	Youth 13–19	0.2
Infants 0.5–1	0.1	Adults 20–49	0.1
Children 1–2	0.15	Adults 50+	0.1
Children 3–5	0.25	Females 13–49 ^c	0.1
Children 6–12	0.3		

^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.

fluoride/day (Levy 1994; Warren and Levy 1999). 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 1994; Warren and Levy 1999).

The dietary fluoride supplement schedule in the US, 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 2006; Table 6). 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 1999; NRC 2006).

Atmospheric fluoride

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. Volcanic 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). 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 US 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 ~ 9000 pounds

or 4100 kg (TRI 2003). Anthropogenic hydrogen fluoride emissions in Canada in the mid-1990s were estimated at 5400 metric tons (5.4 million kg or 11.9 million pounds), of which 75% was attributed to primary aluminum producers (CEPA 1996).

Measured fluoride concentrations in air in the United States and Canada typically range from 0.01–1.65 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 2.5–14,000 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 ~ 600 µg/m³ during the 1981 growing season in a rural inhabited area (Cornwall Island) on the US–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 US, 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 (0.000,06 mg/kg/day) for an adult. In urban areas (< 2 µg/m³), fluoride exposures would be less than 20 µg/day (0.0001–0.002 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 (0.000,01 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-h working day (0.24 mg/kg/day for a 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).

Soil source of fluoride

Fluoride in soil could be a source of inadvertent ingestion exposure, primarily for children. Typical fluoride concentrations in soil in the US range from very low (< 10 ppm) to as high as 3–7% in areas with high concentrations of fluorine-containing minerals (reviewed by ATSDR 2003). Mean or typical concentrations in the US 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

Table 6. Dietary fluoride supplement schedule of 1994.

Age	Fluoride concentration in drinking water, mg/L		
	< 0.3	0.3–0.6	> 0.6
Birth to 6 months	None	None	None
6 months to 3 years	0.25 mg/day	None	None
3–6 years	0.50 mg/day	0.25 mg/day	None
6–16 years	1.0 mg/day	0.50 mg/day	None

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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 0.0025–0.01 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 non-food 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.

Pesticide contributions

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_3AlF_6), is a broad spectrum insecticide that has been registered for use in the US since 1957. Currently, it is used on many food (tree fruits, berries, and vegetables) and feed crops, and on non-food 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 (~ 15.5%, 37%, and 43% of the total available fluoride) (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_2F_2) is a structural fumigant registered for use in the US 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 6803 mg-h/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., Menlo Park, CA) uses the food consumption data from the 1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the US Department of Agriculture (USDA). The 1994–1996 database consists of food intake diaries of more than 15,000 individuals nationwide on two non-consecutive days. A total of 4253 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 5559 children of 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 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 over-estimated (EPA 2004). The dietary fluoride exposure thus estimated ranged from 0.0003–0.0031 mg/kg/day from cryolite, 0.0003–0.0013 mg/kg/day from sulfuryl fluoride, and 0.005–0.0175 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, p. 49), the highest detected fluoride residue in instant tea powder is 898.72 ppm.

Fluorinated organic chemicals

Many pharmaceuticals, consumer products, and pesticides contain organic fluorine (e.g. $-\text{CF}_3$, $-\text{SCF}_3$, $-\text{OCF}_3$). 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 contributes 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 (desethylen-, 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 h after the initial oral dose of ciprofloxacin at 15–25 mg/kg. The presumed steady state (day 7 of repeated dosing) 24-h urinary fluoride concentration was 15.5% higher than the predosing concentration (59 μM vs 51 μM ; or 1.12 ppm vs 0.97 ppm). Another example of limited contribution to serum fluoride concentration from pharmaceuticals was reported for flecainide, an anti-arrhythmic drug. The peak serum fluoride concentration ranged from 0.0248–0.0517 ppm (1.3–2.7 μM) in six healthy subjects (26–54 years old, three males and three females) 4.5 h 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 illustrates 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).

Aluminofluorides and berylliofluorides

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 (Strunecka and Patocka 2002). Fluoroaluminate complexes are the most common forms in which fluoride can enter the environment. Eight per cent 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_3AlF_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; Strunecka 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 flocculant or 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).

Amplified statement

Aluminofluoride and berylliofluoride complexes appear to act as analogs 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; Facanha and Okorokova-Facanha 2002; Strunecka 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; Facanha and Okorokova-Facanha 2002; Strunecka 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. 1950). 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 berylliofluoride complexes can be expected to occur in humans as well as the biological effects that could result.

In other words, the fluoride complex can occupy the terminal end of the molecule by mimicking phosphate. So when AlF or BeF complexes with GDP or ADP—instead of an energy molecule ATP or GTP resulting, a 'dud' is made—a foreign molecule—a hybrid between chemistry and biology. It can't fire. So there will be no energy at the site(s) 'downriver' that are waiting for the energy that fluoride hijacked into anarchy. What damage is met by fluoride interfering with the phosphate fired energy cycle?

Fluorosilicates

Most fluoride in drinking water is added in the form of fluosilicic acid (fluorosilicic acid, H_2SiF_6) or the sodium salt (sodium fluosilicate, Na_2SiF_6), collectively referred to as fluorosilicates (CDC 1993). Of ~ 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. 2007).

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. 2007). 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; 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.

Macek et al. (2006) have also compared blood lead concentrations in children by the 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, 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.

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 $[\text{Si}(\text{OH})_4]$, 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 ($\text{pH} < 5$; 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, 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 $\text{pH} < 6$.

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 $\text{pH} < 5$, 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; 2001b; Lewis and Limeback 1996). Heller et al. (1997; 2000) estimated that a typical infant less than 1 year old who drinks fluoridated water containing fluoride at 1 mg/L would ingest ~ 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. 1995a) 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 per cent 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 0.29–0.38 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 0.32–0.38 mg/day (Levy et al. 1995a); the maximum fluoride intakes ranged from 1.24 (6 weeks old) to 1.73 mg/day (9 months old). Ten per cent of the infants at 3 months old exceeded an intake of 1.06 mg/day.

For a larger group of children ($\sim 12,000$ at 3 months and 500 by 36 months of age; Levy et al. 2001a), 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; $\sim 1\%$ of the children had water sources containing more than 2 mg/L fluoride). For ages 1.5–9 months, $\sim 40\%$ of the infants exceeded a mass-normalized intake level for fluoride of 0.07 mg/kg/day; for ages 12–36 months, $\sim 10\text{--}17\%$ exceeded that level (Levy et al. 2001a).

Levy (2003) 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 0.05–0.06 mg/kg/day at 36 months to 0.03–0.04 mg/kg/day at 72 months; 90th percentile values declined from ~ 0.10 mg/kg/day to ~ 0.06 mg/kg/day (Levy 2003). Singer et al. (1985) reported mean estimated total fluoride intakes of 1.85 mg/day for 15–19-year-old males (based on a market-basket survey and a diet of 2800 calories per day) in a fluoridated area (> 0.7 mg/L) and 0.86 mg/day in non-fluoridated areas (< 0.3 mg/L). Beverages and drinking water contributed ~ 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 non-fluoridated 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 non-fluoridated areas.

Rojas-Sanchez et al. (1999) estimated mean total daily fluoride intakes from foods, beverages, and dentifrice by 16–40-month-old children to be 0.767 mg (0.056 mg/kg) in a non-fluoridated 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 45–57% 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 non-fluoridated 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 non-fluoridated 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 non-water sources are presented in Table 7. 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. (1995). The use of fluoride-containing toothpaste is assumed not to occur during the first year of life. Fluoride supplements are considered separately in Table 7 and are not included in the 'total non-water' column.

Children 1–2 years old have the highest exposures from all non-water source components. The two highest non-water exposure groups are children 1–2 and 3–5 years old, at 0.0389 and 0.0339 mg/kg/day, respectively (Table 7).

Table 7. Total estimated chronic inorganic fluoride exposure from nonwater sources.

Population subgroups	Average inorganic fluoride exposure, mg/kg/day					Total nonwater	Supplement ^c
	Sulfuryl fluoride ^a	Cryolite ^a	ground food ^a	Tooth- paste ^b	Air ^a		
All infants (<1 year)	0.0005	0.0009	0.0096	0	0.0019	0.0129	0.0357
Nursing	0.0003	0.0004	0.0046	0	0.0019	0.0078 ^d	0.0357
Nonnursing	0.0006	0.0012	0.0114	0	0.0019	0.0151	0.0357
Children 1-2 years	0.0013	0.0031	0.0210	0.0115	0.0020	0.0389	0.0192
Children 3-5 years	0.0012	0.0020	0.0181	0.0114	0.0012	0.0339	0.0227
Children 6-12 Years	0.0007	0.0008	0.0123	0.0075	0.0007	0.0219	0.0250
Youth 13-19 Years	0.0004	0.0003	0.0097	0.0033	0.0007	0.0144	0.0167
Adults 20-49 years	0.0003	0.0004	0.0114	0.0014	0.0006	0.0141	0
Adults 50+ years	0.0003	0.0005	0.0102	0.0014	0.0006	0.0130	0
Females 13-49 years ^e	0.0003	0.0005	0.0107	0.0016	0.0006	0.0137	0

^aBased on the exposure assessment by EPA (2004). Background food exposures are corrected for the contribution from powdered or dried tea at 987.72 ppb instead of 5 ppm used in EPA analysis.

^bBased on Levy et al. (1995b), assuming two brushings per day with fluoride toothpaste (0.1 % F) and moderate rinsing. The estimated exposures are: 0 mg/day for infants; 0.15 mg/day for 1-2 years; 0.25 mg/day for 3-5 years; 0.3 mg/day for 6-12 years; 0.2 mg/day for 13-19 years; 0.1 mg/day for all adults and females 13-49 years. The calculated exposure in mg/kg/day is based on the body weights from EPA (2004). For most age groups, these doses are lower than the purported maximum of 0.3 mg/day used for all age groups by EPA (2004).

^cBased on ADA (2005) schedule (Table 6) and body weights from EPA (2004). Note that the age groups here do not correspond exactly to those listed by ADA (2005). The estimated exposures are: 0.25 mg/day for infant and 1-2 years; 0.5 mg/day for 3-5 years, and 1 mg/day for 6-12 years and 13-19 years.

^dIncludes the estimated 0.0006 mg/kg/day from breast milk. Using the higher estimated breast-milk exposure from a fluoridated area (approximately 0.0014 mg/kg/day) results in 0.0086 mg/kg/day for total nonwater exposure.

^eWomen of childbearing age.

These doses are approximately 2.5–3-times those of adult exposures.

The estimated exposures from drinking water are presented in Table 8, using the DEEM-FCID model (version 2.03, Exponent Inc., Menlo Park, CA). The water consumption data are based on the FCID translated from the CSFII 1994–1996 and 1998 surveys and represent an update. The food forms for water coded as ‘direct, tap’; ‘direct, source non-specified’; ‘indirect, tap’; and ‘indirect, source non-specified’ 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 non-tap, which includes four food forms coded as ‘direct, bottled’; ‘direct, others’; ‘indirect, bottled’; and ‘indirect, others’.

Fluoride exposures from drinking water (Table 8) 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 non-tap sources (e.g. bottled water). The assumption for non-tap water concentration is based on the

most recent 6-year national public water system compliance monitoring from a 16-state cross-section that represents ~ 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 surfacewater 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 8 shows that non-nursing 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 ~ 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 9. These values represent the sum of exposures from Tables 7 and 8, assuming fluoride supplements might be given to infants and children up to 19 years old in low-fluoride tap-water scenarios (0

Table 8. Estimated chronic (average) inorganic fluoride exposure (mg/kg/day) from drinking water (all sources).^a

Population subgroups	Fluoride concentrations in tap water (fixed nontap water at 0.5 mg/L)				
	0 mg/L	0.5 mg/L	1.0 mg/L	2.0 mg/L	4.0 mg/L
All infants (<1 year)	0.0120	0.0345	0.0576	0.1040	0.1958
Nursing	0.0050	0.0130	0.0210	0.0370	0.0700
Nonnursing	0.0140	0.0430	0.0714	0.1290	0.2430
Children 1–2 years	0.0039	0.0157	0.0274	0.0510	0.0982
Children 3–5 years	0.0036	0.0146	0.0257	0.0480	0.0926
Children 6–12 years	0.0024	0.0101	0.0178	0.0330	0.0639
Youth 13–19 years	0.0018	0.0076	0.0134	0.0250	0.0484
Adults 20–49 years	0.0024	0.0098	0.0173	0.0320	0.0620
Adults 50+ years	0.0023	0.0104	0.0184	0.0340	0.0664
Females 13–49 years ^b	0.0025	0.0098	0.0171	0.0320	0.0609

^aEstimated 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.

Table 9. Total estimated (average) chronic inorganic fluoride exposure (mg/kg/day) from all sources, assuming nontap water at a fixed concentration^a

Population subgroups	Concentration in tap water (fixed nontap water at 0.5 mg/L)						
	With fluoride supplement		Without fluoride supplement				
	0 mg/L	0.5 mg/L	0 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L
All infants (<1 year)	0.061	0.083	0.025	0.047	0.070	0.117	0.209
Nursing ^b	0.049	0.057	0.013	0.021	0.030	0.046	0.079
Nonnursing	0.065	0.094	0.029	0.058	0.087	0.144	0.258
Children 1–2 years	0.062	0.074	0.043	0.055	0.066	0.090	0.137
Children 3–5 years	0.060	0.071	0.038	0.049	0.060	0.082	0.126
Children 6–12 years	0.049	0.057	0.024	0.032	0.040	0.055	0.086
Youth 13–19 years	0.033	0.039	0.016	0.022	0.028	0.039	0.063
Adults 20–49 years	0.017	0.024	0.017	0.024	0.031	0.046	0.076
Adults 50+ years	0.015	0.023	0.015	0.023	0.031	0.047	0.079
Females 13–49 years ^c	0.016	0.024	0.016	0.024	0.031	0.046	0.075

^aThe estimated exposures from fluoride supplements and total nonwater sources (including pesticides, background food, air, and toothpaste) are from Table 7. The estimated exposures from drinking water are from Table 8. For nonfluoridated areas (tap water at 0 and 0.5 mg/L), the total exposures are calculated both with and without fluoride supplements.

^bThe higher total nonwater exposure of 0.0086 mg/kg/day that includes breast milk from a fluoridated area (footnote in Table 7) 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.

^cWomen of childbearing age.

and 0.5 mg/L). Table 9 shows that, when tap water contains fluoride, non-nursing 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 non-nursing 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 9 for scenarios with 1, 2, and 4 mg/L in tap water are illustrated in Figures 1–3, respectively. Numerical values for the 1-, 2-, and 4-mg/L scenarios are given later in the summary tables (Tables 10–12). Under the assumptions for estimating the exposure, the contribution from pesticides plus fluoride in the air is within 4–10% for all population sub-groups 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 non-nursing 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 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 and 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 ~ 42%, while the contributions from toothpaste and background food are sizable, ~ 18% and 31%, respectively (Figure 1). At 2 mg/L, the drinking-water contribution is raised to ~ 57%, while the contributions from toothpaste and background food are reduced to 13% and 23%, respectively (Figure 2).

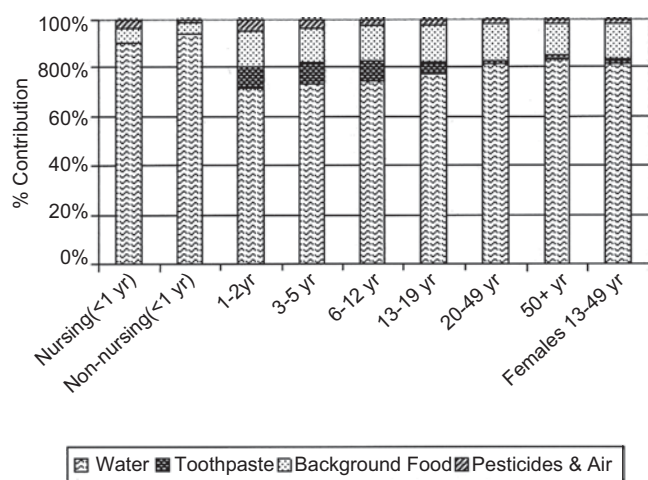


Figure 1. Source contribution to total inorganic fluoride exposure, including fluoride at 1 mg/L in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures 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).

At 4 mg/L, the relative contribution of drinking water continues to increase to ~ 72%, while the contribution from toothpaste and background food are further reduced to ~ 9% and 15%, respectively (Figure 3). As age increases toward adulthood (20+ years), the contribution from toothpaste

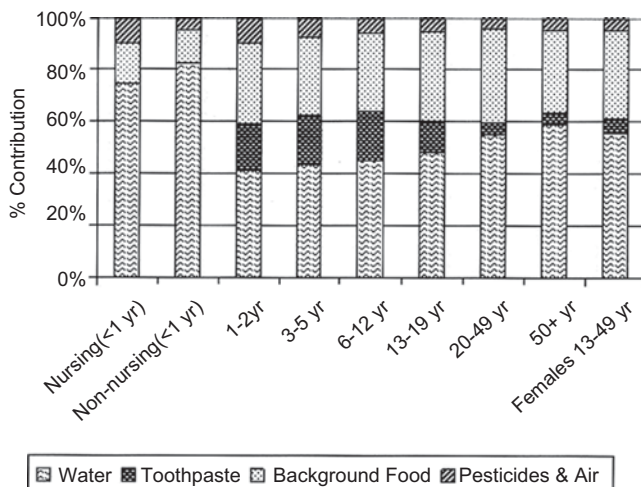


Figure 2. Source contribution to total inorganic fluoride exposure, including fluoride at 2 mg/L fluoride in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The 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).

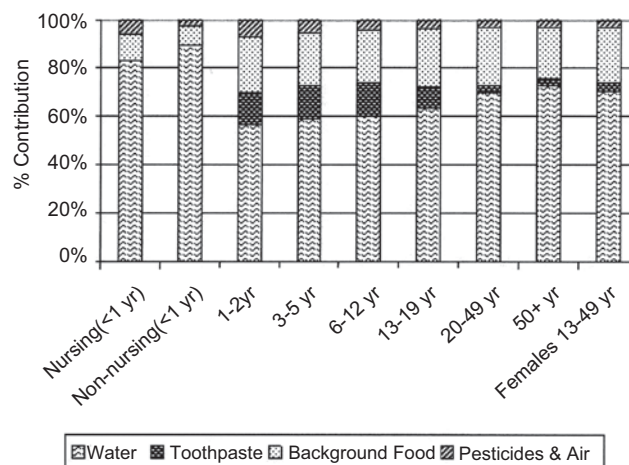


Figure 3. Source contribution to total inorganic fluoride exposure, including fluoride at 4 mg/L in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures as presented in Table 2-11 for the population subgroups are: 0.079 mg/kg/day (nursing infants), 0.258 mg/kg/day (non-nursing 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).

Table 10. Contributions to total fluoride chronic exposure at 1 mg/l in drinking water.

Population subgroups	Total exposure, mg/kg/day	% Contribution to total exposure			
		Pesticides and air	Background food	Tooth-paste	Drinking water
Modeled average water consumer (Tap water at 1 mg/L, nontap water at 0.5 mg/L; Table 2-11)					
All infants (<1 year)	0.070	4.7	13.6	0	81.7
Nursing	0.030	8.9	15.6	0	70.8
Nonnursing	0.087	4.3	13.2	0	82.5
Children 1-2 years	0.066	9.7	31.7	17.4	41.3
Children 3-5 years	0.060	7.4	30.4	19.1	43.1
Children 6-12 years	0.040	5.4	30.9	18.9	44.8
Youth 13-19 years	0.028	4.9	34.8	12.0	48.3
Adults 20-49 years	0.031	4.0	36.3	4.6	55.1
Adults 50+ years	0.031	4.4	32.4	4.6	58.7
Females 13-49 years ^a	0.031	4.4	34.7	5.3	55.6
EPA default water intake, all water at 1 mg/L (1 L/day for 10-kg child; 2 L/day for 70-kg adult; Table 2-12)					
All infants (<1 year)	0.113	2.9	8.5	0	88.6
Nursing	0.109	2.4	4.3	0	92.0
Nonnursing	0.115	3.2	9.9	0	86.9
Children 1-2 years	0.139	4.6	15.1	8.3	72.0
Adults 20-49 years	0.043	3.0	26.7	3.3	67.0
High end of high water intake individuals all water at 1 mg/L (based on intake rates in Table 2-4)					
Athletes and workers	0.084	1.5	13.5	1.7	83.3
DM patients (3-5 years)	0.134	3.3	13.5	8.5	74.7
DM patients (adults)	0.084	1.5	13.5	1.7	83.3
NDI patients (3-5 years)	0.184	2.4	9.9	6.2	81.6
NDI patients (adults)	0.164	0.8	6.9	0.9	91.4

^aWomen of childbearing age.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.

is reduced to ~ 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 ~ 57% at 1 mg/L, 70% at 2 mg/L, and 82% at 4 mg/L.

Data presented in Tables 7–9 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 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 under-estimated. 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 7 represents an average daily consumption of one-half cup of brewed tea or two cups of iced tea. A habitual tea drinker, especially for brewed tea, can be expected to significantly exceed these consumption rates. 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 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 9 are derived from assuming that the non-tap water has a fixed fluoride concentration of 0.5 mg/L, while tap-water concentration varies up to 4 mg/L. Table 13 provides alternative calculations of total exposure by assuming that all sources of drinking water (both tap and non-tap 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 13 can serve as a bounding estimate from the water contribution. The difference in the total fluoride exposure calculated from the two water intake methods

Table 11. Contributions to total fluoride chronic exposure at 2 mg/l in drinking water.

Table 11. Contributions to total fluoride chronic exposure at 2 mg/L in drinking water.					
Population subgroups	Total exposure, mg/kg/day	% Contribution to Total Exposure			
		Pesticides and air	Background food	Tooth-paste	Drinking water
Modeled average water consumer (Tap water at 2 mg/L, nontap water at 0.5 mg/L; Table 2-11)					
All infants (<1 year)	0.117	2.8	8.2	0	89.0
Nursing	0.046	5.8	10.1	0	81.0
Nonnursing	0.144	2.6	7.9	0	89.5
Children 1-2 years	0.090	7.1	23.3	12.8	56.7
Children 3-5 years	0.082	5.4	22.1	13.9	58.6
Children 6-12 years	0.055	3.9	22.4	13.7	60.1
Youth 13-19 years	0.039	3.5	24.5	8.5	63.5
Adults 20-49 years	0.046	2.8	24.7	3.1	69.4
Adults 50+ years	0.047	2.9	21.7	3.0	72.4
Females 13-49 years ^a	0.046	3.0	23.4	3.6	70.1
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)					
All infants (<1 year)	0.213	1.6	4.5	0	93.9
Nursing	0.209	1.3	2.2	0	95.8
Nonnursing	0.215	1.7	5.3	0	93.0
Children 1-2 years	0.239	2.7	8.8	4.8	83.7
Adults 20-49 years	0.071	1.8	16.0	2.0	80.2
High end of high water intake individuals all water at 2 mg/L (based on intake rates in Table 2-4)					
Athletes and workers	0.154	0.8	7.4	0.9	90.9
DM patients (3-5 years)	0.234	1.9	7.7	4.9	85.5
DM patients (adults)	0.154	0.8	7.4	0.9	90.9
NDI patients (3-5 years)	0.334	1.3	5.4	3.4	89.9
NDI patients (adults)	0.314	0.4	3.6	0.5	95.5

^aWomen of childbearing age.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus.

(i.e. EPA defaults vs FCID modeled) varies with different population sub-groups, shown in Table 13. 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 ~ 32–39% higher total exposure than the model estimates. This approximates the 38–45% lower model estimate of total water intake rate (i.e. 19.7 mL/kg/day for 20–49 year olds, 20.7 mL/kg/day for 50+ year olds).

Using EPA's default water intake rate for a child results in ~ 16% higher total exposure than the model estimates for non-nursing 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 13 to those in Tables 7 and 9. 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 non-water sources, as presented in Table 7. The difference between model estimates presented in Table 9 (last three columns) by varying concentrations for tap water alone (with fixed non-tap water at 0.5 mg/L) and estimates using one fluoride concentration for both tap and non-tap waters in Table 13 (first three columns) reflects the contribution from the non-tap-water component. The fluoride exposure estimates presented thus far, regardless of the various assumptions (e.g. the same vs different fluoride concentrations in tap and non-tap water) and different water intake rates (e.g. EPA default vs 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 3). The high-end exposures for these high-water consumption population sub-groups 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 10), 2 mg/L (Table 11), and 4 mg/L (Table 12). 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

Table 12. Contributions to total fluoride chronic exposure at 4 mg/l in drinking water.

Population subgroups	Total exposure, mg/kg/day	% Contribution to total exposure			
		Pesticides and air	Background food	Tooth-paste	Drinking water
Modeled average water consumer (Tap water at 4 mg/L, nontap water at 0.5 mg/L; Table 2-11)					
All infants (<1 year)	0.209	1.6	4.6	0	93.9
Nursing	0.079	3.3	5.9	0	89.0
Nonnursing	0.258	1.4	4.4	0	94.1
Children 1-2 years	0.137	4.7	15.3	8.4	71.6
Children 3-5 years	0.126	3.5	14.4	9.0	73.1
Children 6-12 years	0.086	2.5	14.3	8.7	74.5
Youth 13-19 years	0.063	2.2	15.4	5.3	77.1
Adults 20-49 years	0.076	1.7	15.0	1.9	81.5
Adults 50+ years	0.079	1.7	12.8	1.8	83.7
Females 13-49 years ^a	0.075	1.8	14.3	2.2	81.7
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

^aWomen of childbearing age.

ABBREVIATIONS: DM, diabetes mellitus; NDI, nephrogenic diabetes insipidus

Table 13. 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.^a

Population subgroups	Concentration in all water					
	1 mg/L	2 mg/L	4 mg/L	1 mg/L	2 mg/L	4 mg/L
	Modeled water intake ^b			EPA default water intake ^c		
All infants (<1 year)	0.082	0.151	0.289	0.113	0.213	0.413
Nursing	0.034	0.060	0.111	0.109	0.209	0.409
Nonnursing	0.100	0.186	0.357	0.115	0.215	0.415
Children 1-2 years	0.070	0.102	0.164	0.139	0.239	0.439
Children 3-5 years	0.063	0.093	0.151	NA	NA	NA
Children 6-12 years	0.042	0.062	0.103	NA	NA	NA
Youth 13-19 years	0.030	0.045	0.075	NA	NA	NA
Adults 20-49 years	0.034	0.053	0.093	0.043	0.071	0.128
Adults 50+ years	0.034	0.054	0.096	0.042	0.070	0.127
Females 13-49 years ^d	0.033	0.053	0.092	0.042	0.071	0.128

^aThe estimated exposures from nonwater sources (including pesticides, background food, air, and toothpaste) are from Table 7. No fluoride supplement is included in the total fluoride exposure estimates.^bThe component of drinking-water exposure is estimated from DEEIM-FCID.^cThe 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.^dWomen of childbearing age.

data and assuming a fixed non-tap 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 non-tap waters. Both sets of estimates include the same fluoride exposure from non-water 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 non-tap waters contain the same concentration of fluoride residue as the tap water.

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 under-estimated 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 default water intake rate is likely higher than the average rate for certain population sub-groups (e.g. nursing infants).

The estimates presented in Tables 10–12 show that on a per body weight basis, the exposures are generally higher for young children than for the adults. By assuming that the non-tap water concentration is fixed at 0.5 mg/L, non-nursing 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 (Tables 9–12). The major contributing factor is their much higher model-estimated drinking-water exposure than other age groups (Table 8). The total exposures of non-nursing infants are ~ 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 non-nursing infants, reflecting the higher exposure from non-water sources (Table 7). 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 10–12). These exposures are ~ 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 ~ 2-times the exposure at 2 mg/L and 3-times the exposure at 1 mg/L.

The estimated total daily fluoride exposures for three population sub-groups with significantly high water intake rates are included in Tables 10–12. The matching age groups for data presented in Table 3 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 3 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 ~ 2-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 10–12. 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 1–3).

Assuming that all drinking-water sources (tap and non-tap) 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.

No means to monitor fluoride intake

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).

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 1996; ATSDR 2003). Table 14 gives examples of measurements in humans together with the associated estimates of exposure.

The Centers for Disease Control and Prevention (CDC 2002; 2005) has measured a number of chemicals in blood or urine of members of the US 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). 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 (Whitford 1996). In addition, a significant decrease in fluoride exposure might not be reflected immediately in urine or plasma, presumably because of remobilization of fluoride from resorbed bone.

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 (Rolla 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 vs a non-fluoridated 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 h after use of the dentifrice (Whitford et al. 2005). Whitford et al. (1999b) found that whole saliva fluoride concentrations in 5–10-year-old children were not 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 0.61–1.07).

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 6–7-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 ~ 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 than in toenails in 2–6-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, Correa Rodrigues et al. (2004), in samples from 2–3-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 ~ 4 months later (Correa 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 Gdansk 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. (2004) 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 – 300 ppm (0.19 – 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 1100 – 5300 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 – 2100 ppm in bone ash (0.48 – 2.1 mg/g bone ash in ribs), with concentrations between 3100 – $13,100$ 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 – 1200 ppm in bone ash and in people 'suffering excessive exposure' to fluorides between 7500 – $20,830$ 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 3708 ppm (79-year old with fluoridated water). A 46-year old female with chronic renal failure had a fluoride concentration in bone ash of 3253 ppm (Eble et al. 1992). 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 concentrations in drinking water. However, the ranges 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 addition, 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 considered to be enamel fluorosis and skeletal fluorosis (ATSDR 2003); these are discussed more fully elsewhere. 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 US 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 population 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 ~ 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 is characterized by increased bone mass, increased radiographic density of the bones, and a range of skeletal and joint symptoms; pre-clinical skeletal fluorosis is associated with fluoride concentrations of 3500 – 5500 ppm in bone ash and clinical stages I, II, and III with concentrations of 6000 – 7000 , 7500 – 9000 , and > 8400 , respectively (PHS 1991), although other sources indicate lower concentrations of bone fluoride in some cases of skeletal fluoride. 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 years, 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

Table 14. Summary of selected biomarkers for fluoride exposure in humans.

Fluoride exposure	Number of Persons	Fluoride Concentration	Reference
Urine			
1.2-2.2 mg/day	5	0.8-1.2 mg/day	Teotia et al. 1978
2.5-3.8 mg/day	2	1.2-2.2 mg/day	
8.7-9.2 mg/day	3	3.2-5.8 mg/day	
21.0-28.0 mg/day	2	10.0-11.0 mg/day	
48.0-52.0 mg/day	2	15.0-18.5 mg/day	
1.0 mg/L in drinking water	17	1.5 (0.2) mg/L	Bachinskii et al. 1985
		1.9 (0.3) mg/day	
2.3 mg/L in drinking water	30	2.4 (0.2) mg/L	
		2.7 (0.2) mg/day	
0.09 (range, 0.06-0.11) mg/L in drinking water	45	0.15 (0.07) mg/Lb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	0.62 (0.26) mg/Lb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	1.24 (0.52) mg/Lb	
0.32 mg/L in drinking water	100	0.77 (0.49) mg/Lb	Czarnowski et al. 1999
1.69 mg/L in drinking water	111	1.93 (0.82) mg/Lb	
2.74 mg/L in drinking water	89	2.89 (1.39) mg/Lb	
About 3 mg/day	1	2.30-2.87 mg/day	Whitford et al. 1999a
About 6 mg/day	1	4.40-5.13 mg/day	
7.35 (1.72) mg/dayb	50	9.45 (4.11) mg/Lb	Gupta et al. 2001
11.97 (1.8) mg/dayb	50	15.9 (9.98) mg/Lb	
14.45 (3.19) mg/daya	50	17.78 (7.77) mg/La	
32.56 (9.33) mg/daya	50	14.56 (7.88) mg/La	
0.93 (0.39) mg/dayb	11	0.91 (0.45) mg/Lb	Haftenberger et al. 2001
[0.053 (0.021) mg/kg/dayb]			
1.190 (0.772) mg/day from all sourcesb	20	0.481 (0.241) mg/dayb	Pessan et al. 2005
Plasma			
1.2-2.2 mg/day	5	0.020-0.038 mg/L	Teotia et al. 1978
2.5-3.8 mg/day	2	0.036-0.12 mg/L	
8.7-9.2 mg/day	3	0.15-0.18 mg/L	
21.0-28.0 mg/day	2	0.11-0.17 mg/L	
48.0-52.0 mg/day	2	0.14-0.26 mg/L	
Serum			
1.0 mg/L in drinking water	17	0.21 (0.01) mg/L	Bachinskii et al. 1985
2.3 mg/L in drinking water	30	0.25 (0.01) mg/L	
7.35 (1.72) mg/dayb	50	0.79 (0.21) mg/Lb	Gupta et al. 2001
11.97 (1.8) mg/dayb	50	1.10 (0.58) mg/Lb	
14.45 (3.19) mg/dayb	50	1.10 (0.17) mg/Lb	
32.56 (9.33) mg/dayb	50	1.07 (0.17) mg/Lb	
0.3 mg/L in drinking water: Breastfed infants	48	0.0042 (0.0027) mg/Lb	Hossny et al. 2003
All infants (4 weeks-2 years)	97	0.0051 (0.0030) mg/Lb	
Preschoolers (2-6 years)	100	0.011 (0.0049) mg/Lb	
Primary schoolers (6-12 years)	99	0.010 (0.0042) mg/Lb	
Saliva			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	6.25 (2.44) µg/Lb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	11.23 (4.29) µg/Lb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	15.87 (6.01) µg/Lb	
0.1 mg/L in drinking water	27	1.9-55.1 µg/L	Oliveby et al. 1990
1.2 mg/L in drinking water	27	1.9-144 µg/L	Oliveby et al. 1990
Plaque			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	5.04 (4.60) ppmb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	8.47 (9.69) ppmb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	19.6 (19.3) ppmb	
Hair			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	0.18 (0.07) µg/gb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	0.23 (0.11) µg/gb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	0.40 (0.25) µg/gb	

Table 14. continued on the next page

Table 14. Continued

Fluoride exposure	Number of Persons	Fluoride Concentration	Reference
0.27 mg/L in drinking water and 2.8 µg/m ³ in air	59	1.35 (0.95) µg/gb	Hac et al. 1997
0.32 mg/L in drinking water	53	4.13 (2.24) µg/gb	Czarnowski et al. 1999
1.69 mg/L in drinking water	111	10.25 (6.63) µg/gb	
2.74 mg/L in drinking water	84	14.51 (6.29) µg/gb	
Breast milk			
0.2 mg/L in drinking water	47	0.0053 mg/L (colostrum)	Spak et al. 1983
1.0 mg/L in drinking water	79	0.0068 mg/L (colostrum)	
1.0 mg/L in drinking water	17	0.007 mg/L (mature milk)	
Nonfluoridated community	32	0.0044 mg/L	Dabeka et al. 1986
1 mg/L in drinking water	112	0.0098 mg/L	
22.1 mg/day (mean)	27	0.011-0.073 mg/L	Opinya et al. 1991
0.3 mg/L in drinking water	60	0.0046 (0.0025) mg/Lb	Hossny et al. 2003
Fingernails			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	0.79 (0.26) ppmb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	1.31 (0.49) ppmb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	2.31 (1.14) ppmb	
About 3 mg/day	1	1.94-3.05 mg/kg	Whitford et al. 1999a
About 6 mg/day (after 3.5 months)	1	4.52-5.38 mg/kg	
0.1 mg/L in drinking water	10	0.75-3.53 mg/kg	
1.6 mg/L in drinking water	6	2.28-7.53 mg/kg	
2.3 mg/L in drinking water	9	4.00-13.18 mg/kg	
0.7-1.0 mg/L in drinking water, without fluoride dentifrice	10	2.3-7.3 mg/kg	Corrêa Rodrigues et al. 2004
0.7-1.0 mg/L in drinking water, with fluoride dentifrice (after 4 months)	10	10.1 mg/kg (peak)	
0.004 ± 0.003 mg/kg/day	15	0.42-6.11 µg/g	Levy et al. 2004
0.029 ± 0.029 mg/kg/day	15	0.87-7.06 µg/g	
Toenails			
0.09 mg/L in drinking water		4.2 ppm	Feskanich et al. 1998
1.0 mg/L in drinking water		6.4 ppm	
3 mg/day	1	1.41-1.60 mg/kg	Whitford et al. 1999a
0.7-1.0 mg/L in drinking water, without fluoride dentifrice	10	2.5-5.6 mg/kg	Corrêa Rodrigues et al. 2004
0.7-1.0 mg/L in drinking water, with fluoride dentifrice (after 4 months)	10	9.2 mg/kg (peak)	
0.004 ± 0.003 mg/kg/day	15	0.08-3.89 µg/g	Levy et al. 2004
0.029 ± 0.029 mg/kg/day	15	0.81-6.38 µg/g	
Teeth			
Normal	NA	190-300 ppm (total ash)	Roholm 1937
Cryolite workers	5	1,100-5,300 ppm (total ash)	
Enamel (0.44-0.48 µm depth)			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	1,549 (728) ppmb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	2,511 (1,044) ppmb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	3,792 (1,362) ppmb	
Enamel (2.44-2.55 µm depth)			
0.09 (range, 0.06-0.11) mg/L in drinking water	45	641 (336) ppmb	Schamschula et al. 1985
0.82 (range, 0.5-1.1) mg/L in drinking water	53	1,435 (502) ppmb	
1.91 (range, 1.6-3.1) mg/L in drinking water	41	2,107 (741) ppmb	
Enamel			
0.7 or 1.0 mg/L in drinking water	30	0-192 µg/g	Vieira et al. 2005
Dentin			
0.7 or 1.0 mg/L in drinking water	30	59-374 µg/g	Vieira et al. 2005
Bones			
Normal	NA	480-2,100 ppm in bone ash (ribs)	Roholm 1937
Cryolite workers	2	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)	

Table 14. continued on the next page

Table 14. Continued

Fluoride exposure	Number of Persons	Fluoride Concentration	Reference
0.1-0.4 mg/L in drinking water	33	326-2,390 ppm in bone ashc	Zipkin et al. 1958
1.0 mg/L in drinking water	5	1,610-4,920 ppm in bone ashd	
2.6 mg/L in drinking water	27	1,560-10,800 ppm in bone ashe	
4.0 mg/L in drinking water	4	4,780-11,000 ppm in bone ashf	
< 0.2 mg/L in drinking water since infancy	8	1,379 (179) ppm in bone ashg	Eble et al. 1992
1 mg/L in drinking water at least 23 years or since infancy	9	1,775 (313) ppm in bone ashg	
0.27 mg/L in drinking water and 2.8 µg/m ³ in air	59	625.7 (346.5) ppmb,h	Hac et al. 1997
0.7 or 1.0 mg/L in drinking water	30	0-396 ppmi	Vieira et al. 2005

^aPrevious exposure of 30-38 mg/day, 2-5 years before study.

^bMean and standard deviation.

^cReported as 0.019-0.119% in bone, with ash content of 43.2-68.4%.

^dReported as 0.100-0.238% in bone, with ash content of 45.9-62.2%.

^eReported as 0.092-0.548% in bone, with ash content of 32.7-66.7%.

^fReported as 0.261-0.564% in bone, with ash content of 44.3-62.8%.

^gMean and standard error of the mean.

^hReported as µg fluoride per gram bone; appears to be dry weight of bone, not bone ash. ⁱMeasured by Instrumental Neutron Activation Analysis; appears to be wet weight of bone.

ABBREVIATION: NA, not available.

factors such as dietary calcium deficiency involved in addition to fluoride intake (Teotia et al. 1998).

Hodge and Smith (1965) summarized a number of studies of skeletal fluorosis, including two that indicated affected individuals in the US 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 US'. 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 US (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 3.9-8.0 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 were reported in the US. 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 vs exposures in childhood vs 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

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 (1994) attempted to track down the origin of the estimate of 0.05-0.07 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 9 shows the average intake of fluoride from all sources estimated in this report, with 1 mg/L in drinking water; Table 8 shows the average intake of fluoride from drinking water alone, 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 (2000) estimates of community water consumption by consumers with an average intake, if that water is fluoridated:

- Children less than 6 months old have an intake at or above 0.05–0.07 mg/kg/day;
- 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 and the youngest children (< 1 year) intake might exceed 0.05–0.07 mg/kg/day at all concentrations of water fluoridation; and
- 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 include only the fluoride contribution from 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 9 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;
- Children not on supplements, non-nursing infants with fluoride in tap water at ≥ 0.5 mg/L will exceed 0.05–0.07 mg/kg/day for typical exposures; and
- 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 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 for exposure research

- 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 sub-groups 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 sub-groups.
- 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 re-evaluated 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, and

- reporting data in terms of individual correlations between intake and effect, differences in sub-groups, 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.
- The NRC concluded that EPA's safety standard for fluoride is not safe and 'should be lowered.' According to the NRC, EPA's 'safe' standard (4 ppm) puts a person at increased risk for both tooth and bone damage ('severe dental fluorosis' and bone fracture).

Fluoride's impact on organs and function

Our review of the literature on the subject of the toxicity of fluoride has taken great advantage of the NRC's *Fluoride in Drinking Water, A Scientific Review of EPA's Standards* (2006). It has been shown that the questions concerning the safety and effectiveness of the national program to fluoridate the public water supply have been long-posed, yet remain unanswered. The fact that these questions remain unanswered is not due to a lack of available data on the subject. Rather, the facts show effectiveness and safety concerning the great experiment of adding a contaminant to the water supply. It has been stated that if fluoride is not responsible for lowered incidence of dental caries, then there is no other purpose that has been stated for its existence in public water.

As a practicing doctor treating a wide range of musculoskeletal complaints and injuries, I have personally witnessed a change in the physiology of patients. Without being able to determine the intake or the concentration of fluoride and its various forms, in my patient's or my own, diet, the ability to accurately diagnose and treat is impaired, interfered with, and violated. This is stated solely from a practicing doctor's perspective—if my prescription for care is shown to be ineffective, why would I continue to render it? If it was thought that caries would be prevented by adding fluoride to the water, and we learned that it did not work, it would be expected that in a day when political pressure would dictate reducing wasteful government spending, that an unsuccessful program like water fluoridation, and all its controversy, would be readily and summarily dismissed. Should this not

happen, in such a favorable climate for it to happen, then another reason for its continued operation would need to be found.

It can be seen from the graph of the WHO statistics on caries reduction, measured by DMFT, decayed, missing, or filled teeth, that the reduction in dental caries worldwide demonstrates a non-fluoride axis. Of the 18 nations taking part in the study, all showed consistent steady declines in DMFT scores over a 30 year period—yet only four were fluoridated. In light of the next section, which discusses the damage done by fluoride to living tissue, we may be prompted into taking protective action. This, too, is stated from a doctor's perspective, it is requested that in order for me to more effectively treat my patients, that this terribly invasive, ubiquitous poison be removed from my patient's physiology in all its forms. It is a variable that is a known toxin, an enzyme disruptor, that is 'addicted' to calcium-bonding, favors 'nasty'-bonding with aluminum, increases toxicity of heavy metals like lead, and readily crosses both lungs and GIT. Fluoride comes into contact with the body in many unknown and hidden ways, air, water, food, drugs, cleaners, etc., in unknown and uncontrollable quantities.

Freedom of choice

If people want to purchase fluoride and utilize it for their purposes, they have a right-to-choose and are free to do so in the healthcare marketplace. Meanwhile, there is no justification for fluoride's presence in unknown quantities in uncontrollable amounts in undisclosed products, especially in public water. Regarding fluorine and all its forms, there is clearly a need for truth in labeling.

Effects of fluoride on teeth

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 (NRC 2006).

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 sub-surface 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 (NRC 2006).

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 6–8 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; NRC 2006).

Mechanism of impairment

Dental enamel is formed by matrix-mediated biomineralization. Crystallites of hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) 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 (NRC 2006).

Are teeth a good biomarker?

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 (1942) 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.'

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 discoloured and is prone to fracture and wear (ATSDR 2003).
- 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).
- 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).
- With more severe forms of fluorosis, caries risk increases because of pitting and loss of the outer enamel. (Levy 2003).
- ... 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; 2006).

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 Reprogel 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. 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). However, no systematic studies of tooth eruption have been carried out in communities exposed to fluoride at 2–4 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 1985; PHS 1991; IOM 1997; ADA 2006). 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, although 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 US, 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, ~ 10% on average, among children in US 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 US, 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 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 2006). Between 25–50% of US 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.

For all age groups listed in Table 15, 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). Thus, the exposure estimates above also showed that the IOM limits would be exceeded at 2 mg/L for non-nursing infants at the average water intake level (Table 11).

Specifically, as described in above (Tables 11 and 12), non-nursing 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 10). 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 (2006) 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 US 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-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 US populations are available. Past evidence indicated an incidence range of 4–15% (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 US communities with fluoride concentrations higher than 1 mg/L. These studies should focus

Table 15. Tolerable upper fluoride intakes and percentiles of the U.S. water intake distribution, by age group.

Age Group	Tolerable upper intake (IOM 1997)		Water intake, mL/day (EPA 2004)	
	Fluoride, mg/day	Water, mL/day (at 4 mg/L)	50th Percentile	75th Percentile
0-6 months	0.7	175	42	585
7-12 months	0.9	225	218	628
1-3 years	1.3	325	236	458
4-8 years	2.2	550	316a	574a

^aAges 4-6 years. For ages 7-10 years, the 50th percentile is 355 mL/day and the 75th percentile is 669 mL/day.

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.

Fluoride and 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 $\text{Ca}_{10}(\text{PO}_4)_6\text{OH}_2$. 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 (CO_3^{2-}) replace some of the 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) (NRC 2006). 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 AlF_3 or AlF_4^- . These forms (mostly AlF_3) have been purported to cross the intestine and enter cells (Powell and Thompson 1993). Once inside a bone cell the AlF_x form appears to activate a specific protein tyrosine kinase through a G protein and evoke downstream signals. A more complete discussion of this process is presented in a later section of this chapter (NRC 2006). 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. 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 non-linear 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 4-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 ~ 20 years.

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, micro-architecture,

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; Sogaard et al. 1994; 1995; 1997; Zerwekh et al. 1996); 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, (pg 134); NRC 2006).

Fluoride's effect 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, multi-nucleated 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 (NRC 2006).

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 pre-clinical stage and three clinical stages that characterize the severity.

- The pre-clinical 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 (NRC 2006). In patients with reduced renal function, the potential for fluoride accumulation in the skeleton is increased. It has been known for many years that people with renal insufficiency have elevated plasma fluoride concentrations compared with normal healthy persons (Hanhijarvi 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 4–8 L of water containing fluoride at 2–3 mg/L (Sauerbrunn et al. 1965; Juncos and Donadio 1972), at least 3 L/day at 2–3 mg/L (Johnson et al. 1979), or 2–4 L/day at 8.5 mg/L (Lantz et al. 1987) to become symptomatic (NRC 2006).

Overall, the committee finds that the predicted bone fluoride concentrations that can be achieved from lifetime exposure to fluoride at 4 mg/L (10,000–12,000 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 US. 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 US residents who drink water with fluoride at 4 mg/L. The condition does not appear to have been systematically investigated in recent years in US 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 (NRC 2006). 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 (NRC 2006).

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 (NRC 2006). 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 (NRC 2006, p. 180).

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, post-menopausal women, people with altered acid balance), to better understand the risks of musculoskeletal effects in these populations.

Sexual reproduction and embryology, 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 (NRC 2006). Two early papers (Rapaport 1957; 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 sub-set 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 1957) 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 (NRC 2006).

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 (NRC 2006).

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 (NRC 2006).

Neurotoxicity and neurobehavioral effects

Cognitive effects

Several studies from China have reported the effects of fluoride in drinking water on cognitive capacities (Li et al. 1995; Zhao et al. 1998; 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 (aged 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 mg/L), and the low-fluoride area (Xinhuai) 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 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 ± 1.95 mg/L in Wamiao and 1.11 ± 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 ± 13.00 ; range, 54–126) than that in Xinhuai (100.41 ± 13.21 ; range, 60–128) (NRC 2006).

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 4. A comparable illustration of the IQ scores of males is shown in Figure 5. 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; NRC 2006).

A study conducted by Lu et al. (2003a) in a different area of China also compared the IQs of 118 children (aged 10–12) living in two areas with different fluoride concentrations in the water (3.15 ± 0.61 mg/L in one area and 0.37 ± 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 ± 2.57 mg/L in the high-fluoride area and 1.43 ± 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 ± 20.45) than in children in the low-fluoride area (103.05 ± 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 (aged 7–14) living 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

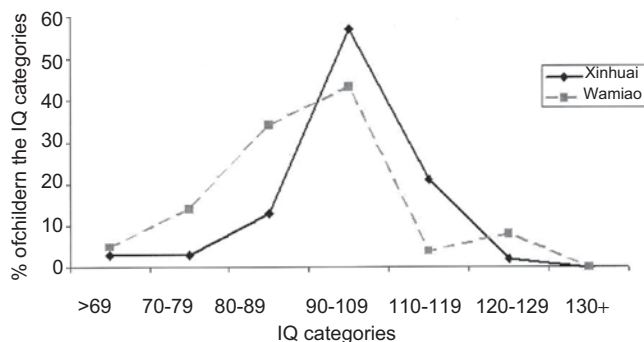


Figure 4. Distribution of IQ scores from females in Wamiao and Xinuai. SOURCE: data from Xiang et al. 2003a.

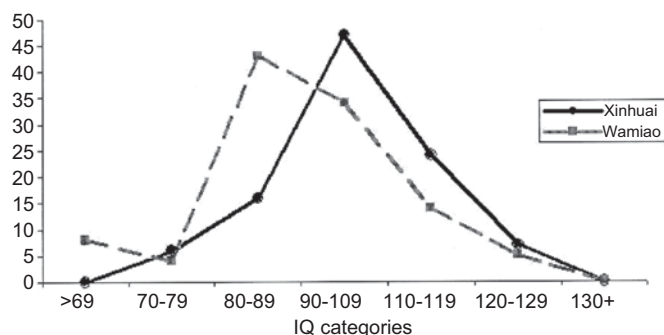


Figure 5. Distribution of IQ scores from males in Wiamiao and Xinuai. SOURCE: data from Xiang et al. 2003a.

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% of the children (NRC 2006).

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 (aged 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 (NRC 2006).

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. 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; NRC 2006).

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 (NRC 2006).

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 (NRC 2006).

Silicofluoride effects

It has been suggested that the silicofluorides used to fluoridate drinking water behave differently in water than other fluoride salts and produce different biological effects. For example, adding sodium silicofluoride (Na_2SiF_6) or fluoro-silicic acid (H_2SiF_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 (NRC 2006).

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 1.2–3 mg/L, reaction times and visuospatial abilities can be impaired.

These changes would act to reduce the tested IQ scores. Such non-cognitive 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 pre-frontal 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 (NRC 2006).

An interesting set of calculations was made by Urbansky and Schock (2000) —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 (NRC 2006).

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 ~ 3-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 (NRC 2006). 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 (NRC 2006). 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 (AlFx). 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 3500 French men and women above the age of 65 (Jacqmin et al. 1995), 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 phospholipids metabolism and/or reductions in the biological energy available for normal brain functions. In addition, the possibility exists that chronic exposure to AlFx 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 O₂ 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; NRC 2006).

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 AlF₃-treated rats. Areas CA3 and CA4 were the most affected regions of the hippocampus (NRC 2006).

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 (NRC 2006).

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 nAChR α 7 sub-units were found in the brains of rats from both treatment groups, but only the brains of the 100-mg/L group had diminished in AChR α 4 sub-units 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; NRC 2006).

Findings

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 AlFx binds to GDP and ADP altering their ability to form the triphosphate molecule essential for providing energies to cells in the brain. Thus, AlFx 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 (NRC 2006).

Studies of rats exposed to NaF or AlF₃ 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) (NRC 2006).

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.
- 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.

Fluoride and hormones

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. 2000; 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' (p. 224). McDonagh et al. (2000) 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 (NRC 2006).

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 (Sundstrom 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 (alone) is considerably smaller and does not appear to displace iodide in the transporter (NRC 2006).

Animal studies

A number of studies have examined the effects of fluoride on thyroid function in experimental animals or livestock. 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. 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 (NRC 2006).

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, together with the approximate intakes or physiological fluoride concentrations that have been typically associated with them thus far. 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 Tables 10–12 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 (NRC 2006).

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 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 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 and with the variability in intake, especially for humans (NRC 2006).

Thyroid

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; 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 (NRC 2006). 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 US (CDC 2002; Larsen et al. 2002) could contribute to increased toxicity of fluoride for some individuals (NRC 2006).

Parathyroid

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 US 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 (NRC 2006).

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; 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 (NRC 2006).

Summary

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 (NRC 2006).

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 pre-existing 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, and
- 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 aluminium 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 sub-groups, and differences in percentages of individuals showing an effect and not just differences in group or population means, and
 - 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 US.

Major areas for investigation include the following:

- thyroid disease (especially in light of decreasing iodine intake by the US 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 (NRC 2006).

Gastrointestinal, renal, hepatic, and immune system effects of fluoride

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. 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 1.0–5.0 mmol/L (20–100 mg/L), applied to the stomach mucosa for at least 15 min, is the threshold for effects on the function and structure of the tissue (Whitford 1996). 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 water 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 (NRC 2006).

The primary symptoms of GI injury are nausea, vomiting, and abdominal pain. Such symptoms have been reported in case studies (Waldbott 1956; Petraborg 1977) and in a clinical study involving doubleblind 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 non-fluoridated water. A pharmacist prepared solutions of sodium fluoride (NaF) and sodium silicofluoride (Na_2SiF_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 (NRC 2006).

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 (NRC 2006).

Animal studies 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 1996), and cause cell death and desquamation of the GI tract epithelium (Easman et al. 1984; Pashley et al. 1984; Susheela and Das 1988; Kertesz et al. 1989; NTP 1990; Shashi 2003; NRC 2006).

Because fluoride is a known inhibitor of several metabolic intracellular enzymes, it is not surprising that, at very high exposures, there is cell 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 (NRC 2006).

Kidneys

The kidney is the organ responsible for excreting most of the fluoride. It is exposed to concentrations of fluoride ~ 5-times higher than in other organs, as the tissue/plasma ratio for the kidney is ~ 5:1, 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:

- 1) Can long-term ingestion of fluoride in drinking water at 4 mg/L contribute to the formation of kidney stones?
- 2) What are the mechanisms of fluoride toxicity on renal tissues and function?
- 3) 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? (NRC 2006).

Does fluoride contribute to kidney stone formation?

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 (Juuti and Heinonen 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 3.5–4.9 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 (NRC 2006).

Kidney-impaired patients

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. 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; NRC 2006).

Liver system

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; NRC 2006).

Immune system

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 (NRC 2006).

Nevertheless, patients who live in either an artificially fluoridated community 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. 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 (NRC 2006). 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, p. 294), 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' (NRC 2006).

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 ~ 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 (NRC 2006).

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 16 in NRC (2006). 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 16 in NRC (2006). 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, AlF₃ 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 (NRC 2006).

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 (NRC 2006).

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 impairments 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 (NRC 2006).

Genotoxicity and carcinogenicity of fluoride

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

Table 16. Effects of fluoride on immune system cells.

Species	Study	Findings	Application/Proposed Mechanisms	Comments	Reference
In vitro					
Human	Metabolism factors measured in cultured PMNs incubated with mM concentrations of fluoride.	Significant inhibition of PMN metabolic activity at 0.1 mM fluoride for O_2 generation. Activity was also inhibited at 0.5 mM for $^{14}CO_2$ release from labeled glucose and at 1.0 mM for nitroblue tetrazolium-reduction.	Inhibition was primarily due to suppression of nonoxidative glucose metabolism. Peak effect was at 20mM, a lethal dose to the cells.		Gabler and Leong 1979
Human	Leukocyte capillary migration inhibition assay.	8% inhibition with 0.5ppm fluoride and 20% inhibition with 20ppm fluoride.		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.	Gibson 1992
Various	Evaluated signal transduction in cultured macrophages exposed to NaF with or without aluminum.	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 $AlCl_3$ or deferoxamine.	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.		Goldman et al. 1995
Human	Cell migration assay and micro-pore filter assay used to assess effect of NaF on locomotion and chemotaxis of human blood leukocytes.	Significant reduction in chemotaxis and locomotion observed with 1 mM fluoride.		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.	Wilkinson 1983
Human	Cultured neutrophils treated with fluoride.	Fluoride activated diacylglycerol generation and phospholipase D activity. Increased diacylglycerol mass, with kinetics similar to superoxide generation.	Data are consistent with the activation of phosphatidic acid and diglyceride generation by both phospholipase independent and independent mechanisms.		Olson et al. 1990
Human	Electroporameabilized neutrophils treated with fluoride.	O_2 production was increased by electroporameabilization. That effect was antagonized by GDP[(β -S), required Mg^{2+} , and was blocked by staurosporine and H-7.	Supports the hypothesis that fluoride activates G protein, most likely Gp, by interacting with the nucleotide-binding site on the G subunit.		Hartfield and Robinson 1990

Table 16. continued on next page

Table 16. Continued

Species	Study	Findings	Application/Proposed Mechanisms	Comments	Reference
Human	Adherence assay of PMNs cultured with 0.0625-4.0 μ M with or without autologous serum.	No effect in the absence of serum. With serum, adherence significantly decreased at 0.5 μ M. Decrease was 1.1% at 0.125 μ M and 52.7% at 1.5 μ M.	Effect is not direct and is probably modulated by a seric factor.	Concentrations of fluoride tested are similar to those found in blood.	Gomez- Ubric et al. 1992
Human	Promyelocyte HL-60 cells treated with 0.5 mM NaF for 0-4 days.	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.	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 PGF2.		Kawase et al. 1996
Human	Blood lymphocytes incubated with NaF at 0.31, 0.62, or 1.2 mM.	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 ($P < 0.01$). 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.	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.		Loftenius et al. 1999
Human	CD34 ⁺ cells isolated from umbilical cord blood were incubated with 1, 10, and 50 mM NaF for 30 and 120 minutes.				Machalinski et al. 2000
Rat	Liver macrophages treated with fluoride.	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.	Calcium-dependent protein kinase C appears to be involved in fluoride's action on liver macrophages.		Schulze-Specking et al. 1991
Mouse	Cultured lymphocytes treated with NaF and AlCl_3 .	With NaF, there was a breakdown of polyphosphoinositides, decreased production of phosphoinositols, increased cytosolic Ca^{2+} , and start of phosphorylation of the T-cell receptor. Effects were potentiated by addition of AlCl_3 .	The active moiety is AlF_4^- . AlF_4^- induced effects were insensitive to cyclic adenosine monophosphate.		O'Shea et al. 1987

Table 16. continued on next page

Table 16. Continued

Species	Study	Findings	Application/Proposed Mechanisms	Comments	Reference
Mouse	Bone marrow progenitor cells cultured with 0.1-0.5 mM NaF.	Upregulation in the activities of intracellular enzymes (LDH, (3-glucuronidase, acid phosphatase), cellular reduction of nitroblue tetrazolium, and nitric oxide production.	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.		Oguro et al. 2003
In vivo					
Rabbit	Rabbits immunized with 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 [³ H]thymidine and [¹⁴ C]leucine incorporation.	NaF inhibited antibody formation and had a threshold of 0.78 ppm in circulation. DNA and protein synthesis were also inhibited.	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
Rat	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.	Significant increase in surface immunoglobulin expression on lymphocytes from the Peyer's patches and mesenteric lymph nodes.	Microclerations 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.	Butler et al. 1990
Rat	0.1, 0.2, and 0.4 mg of fluoride administered intratracheally.	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.			S. Hirano et al. 1999
Mouse	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.	Suppression of pulmonary bacterial activity against <i>Staphylococcus aureus</i> 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 .	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

ABBREVIATIONS: BFU-E, burst forming unit of erythrocytes; CFU-GM, colony-forming unit of granulocyte-macrophages; GDP[β -S], guanosine 5' -[[β -thio]diphosphate; INF- γ , interferon γ ; LDH, lactate dehydrogenase; PGE₂, prostaglandin E; PHA, phytohemagglutinin; PMN, polymorphonuclear leukocyte.

Table 17. Typical fluoride concentrations of major types of drinking water in the United States.

Source	Range, mg/L ^a
Municipal water (fluoridated)	0.7-1.2
Municipal water (naturally fluoridated)	0.7-4.0+
Municipal water (nonfluoridated)	<0.7
Well water	0-7+
Bottled water from municipal source	0-1.2
Spring water	0-1.4 (usually <0.3)
Bottled "infant" or "nursery" water	0.5-0.8
Bottled water with added fluorideb	0.8-1.0
Distilled or purified water	<0.15

^aSee text for relevant references.^bOther than "infant" or "nursery" water.

events or by unmasking malignant cells that previously were in non-dividing states. Osteosarcoma is a rare disease, with an overall annual incidence rate of ~ 0.3 per 100,000 in the US (Schottenfeld and Fraumeni 1996). The age of diagnosis is bimodal with peaks before age 20 and after age 50 (NRC 2006). 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] 1.8-6). Mahoney et al. (1991) generated bone cancer and osteosarcoma incidence rate ratios for the years 1975-1987 for fluoridated and non-fluoridated 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 (NRC 2006).

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=0.84-2.84). The analogous rate for females was 1.37 (95% CI=0.51-3.70). Yang et al. noted statistically significant RRs in females for bladder cancer (RR=2.79, 95% CI=1.41-5.55; for males RR=1.27, 95% CI=0.75-2.15) (NRC 2006).

Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed. 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 (NRC 2006). 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 (NRC 2006).

The 1993 NRC review concluded that the increase in osteoma in male and female mice (Maurer et al. 1993) was related to fluoride treatment. 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; NRC 2006).

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 sub-populations that are prone to accumulating fluoride in their bone (NRC 2006).

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 (NRC 2006).

An immediate means to eliminate the damage being reported here to the cells, organs and tissues of all the species inhabiting this planet is to stop the contamination by fluoride and its dangerous combinations and applications. Certainly, the information contained in this review is more than sufficient in weight when placed on the scale of balance to yield a decision concerning the question of adding this to the public water supply, where all control of dosage is lost by the consumer and the doctor.

This toxin added to public water must begin to be labeled accurately and truthfully, from all the sources from which the human and other life forms are exposed. There remains no health justification for delay. This information is already 65 years overdue.

Conclusion

For nearly three-quarters of a century, fluoride has been lauded as the modern savior of teeth and replacer of bones. It now appears that those hopes and expectations remain unmet. In the next century, we will be faced with the task of corralling a stampede of exposures that have resulted from unlocking fluoride from its containment and releasing it from its sequestered resting place into the very lifeline's of the Earth's and Man's ecology. The uncontrolled contamination by fluoride, the worst of all corrosive reactants, is likely to be seen as the worst mistake man has made in his quest to master everything. We are now faced with an impossible task of trying to identify all the end-points and target organs and to attempt to contain this ill-tempered tiny halogen more than 75 years since it has escaped its confinement by floating up the smokestacks of the aluminum-manufacturing, phosphate-mining, and coal-burning 'barns'.

Making this task even more difficult is an overall perception, embedded deeply into the psyche by decades of false reporting and disinformation, that fluoride is a 'god-send' and is one of the miracles of modern manufacturing, chemistry, and pharmacology. Examining the destruction caused by fluoride, it now appears that nothing could be further from the truth.

A fresh evaluation of the role of fluorine and its fluorides is necessary and long over-due. What we know now about fluorine and its action clearly prompts us to begin to adapt to this newly-identified challenge to our personal and global health and well-being. Fluoride demands immediate reconsideration. To protect the consuming public, fluoride must be completely identified, quantified, and labelled in all its applications, so that monitoring of exposure to fluoride

is possible for individuals. The data offered here in the NRC report demonstrate the acute need to monitor fluoride exposure for all kidney patients.

Non-fluoride axis of declining tooth decay trends

From the work conducted by the World Health Organization (WHO) comparing fluoride and non-fluoride countries, it is clear that fluoride can not be the reason for the reduction of dental disease (see Figure 6). Other explanations must be sought.

Universal decline in tooth decay in the Western world

Although the prevalence of caries varies between countries, levels everywhere have fallen greatly in the past three decades, and national rates of caries are now universally low. This trend has occurred regardless of the concentration of fluoride in water or the use of fluoridated salt, and it probably reflects use of fluoridated toothpastes and other factors, including perhaps aspects of nutrition (Cheng et al. 2007).

In most European countries, where community water fluoridation has never been adopted, a substantial decline in caries prevalence has been reported in the last decades, with reductions in lifetime caries experience exceeding 75% (Izzo et al. 2007). All graphs of tooth decay trends for 12 year olds in 24 countries, prepared using the most recent World Health Organization data, show that the decline in dental decay in recent decades has been comparable in 16 non-fluoridated countries and eight fluoridated countries which met the inclusion criteria of having (i) a mean annual per capita income in the year 2000 of US\$10,000 or more, (ii) a population in the year 2000 of greater than 3 million, and (iii) suitable WHO caries data available. The WHO data do not support fluoridation as being a reason for the decline in

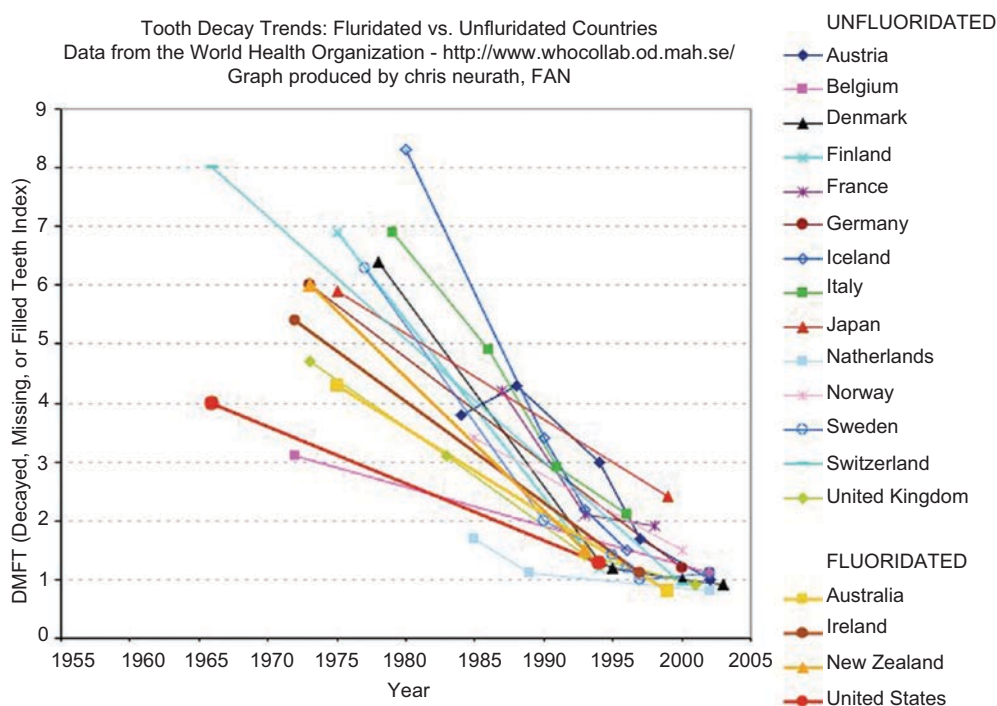


Figure 6. Declining global tooth decay trends demonstrate non-fluoride axis.

dental decay in 12-year olds that has been occurring in recent decades (Neurath 2005).

It is remarkable ... that the dramatic decline in dental caries which we have witnessed in many different parts of the world has occurred without the dental profession being fully able to explain the relative role of fluoride in this intriguing process. It is a common belief that the wide distribution of fluoride from toothpastes may be a major explanation, but serious attempts to assess the role of fluoridated toothpastes have been able to attribute, at best, ~ 40–50% of the caries reduction to these fluoride products. This is not surprising, if one takes into account the fact that dental caries is not the result of fluoride deficiency (Aoba and Fejerskov 2002, p. 165).

Recommendations: Minimize ingested fluoride

In consideration of the currently understood mechanisms of cariostasis and fluorosis, our efforts should be focused on minimizing levels of ingested fluorides. The control of fluoride levels in infant formulas, the recent reductions in the fluoride supplement schedule, and the calls for lower fluoride pediatric toothpastes are all laudable efforts. We cannot, however, ignore water fluoridation as a major source of ingested fluoride.

Fluoridated water unsafe for infant formula

When infants are formula-fed, parents should be advised to reconstitute or dilute infant formula with deionized water (reverse osmosis, distilled, or low-fluoride bottledwater) in order to reduce the amount of systemically ingested fluoride.

We recommend use of water with relatively low fluoride content (e.g. 0–0.3 ppm) as a diluent for infant formulas and recommend that no fluoride supplements be given to infants.

Breastfeeding of infants should be encouraged, both for the many documented, general health benefits and the relative protection against ingestion of excessive fluoride from high quantities of intake of fluoridated water used to reconstitute concentrated infant formula early in infancy.

Use of powder concentrate would be recommended only for those with low-fluoride water (Levy 1995). To limit fluoride intakes to amounts < 0.1 mg/kg/day, it is necessary to avoid use of fluoridated water (around 1 ppm) to dilute powdered infant formulas (Buzalaf 2001).

Our results suggest that the fluoride contribution of water used to reconstitute formulas increases risk of fluorosis and could be an area for intervention ... Supporting long-term lactation could be an important strategy to decrease fluorosis risk of primary teeth and early developing permanent teeth (Marshall 2004).

The recommendation is that bottled or deionized water be used instead (of fluoridated water) to dilute the formula (Ekstrand 1989).

Ingestion of fluoride from toothpaste should be reduced

To reduce the risk of fluorosis, it has been suggested that use of higher concentration of fluoride dentrifices by pre-school

children be avoided, that only small quantities of paste be used under parental direction and supervision, that further development and testing of lower concentration fluoride dentrifices be encouraged, and that dentrifice tubes dispense smaller quantities so that inappropriate eating of fluoride dentrifice is avoided (Levy 1999).

“WARNING: Keep out of reach of children under 6 years of age. If you accidentally swallow more than used for brushing, seek professional help or contact a poison control center immediately.” Mandated FDA warning on all toothpaste containing fluoride.

We recommend that dentists who are considering prescribing dietary fluoride supplements for those with non-fluoridated water inquire about young children’s fluoride exposure from all important sources, including dentrifice, infant formula (type, brand, and quantity), water (sources, quantities, and filtration system), and beverages (including specific juices and juice-flavored drinks) (Kiritry et al. 1996; NRC 2006).

Poisoned research?

Has the extreme reactivity, ubiquitous presence, and power of fluoride exerted an unrecognized and therefore unaccounted for, role in the laboratory? How much work has been conducted in the presence of fluoride acting as an unmeasured variable? There is a strong possibility that any work which employed water containing an unknown amount of fluoride, that the research outcomes may be invalid. Such research could require a re-evaluation due to the presence and concentration of fluoride in the culture or growth media. Here lies a highly-relevant fact—from which the aftershocks that should follow a realization of this magnitude—it may indicate that much of what has been accepted as a or ‘the’ mechanism of action for any reaction or process, may be false. If fluoride was present and unaccounted for, it likely was involved in the mechanism of action. Fluoride does not play a passive role. It is the most reactive of all elements. Due to its raw power and small size, wherever fluoride is found—in all environments and in all applications, fluoride is certain to exert its affect. If an effect was found in the evaluation of the data rendered by an experiment, and if that data was not factored or considered in terms of fluoride’s unmatched reactivity, strength, and corrosive properties, then that data erroneously ascribed fluoride’s influence to another, likely innocent, or less-potent, vector. The point being that unaccounted-for fluoride likely taints, ruins, and invalidates the observed outcomes and their applicability. Fluoride could be terribly misleading when searching for explanations, vectors and/or mechanisms.

The following areas of research have been identified through this investigation:

- 1) *Air born vs water born vectors: Inhalation vs ingestion.* Investigate the difference between these two routes of entry into the body. A comparison study.
- 2) *Respiratory vs circulatory.* What can we learn from an inquiry histopathologically into the status of the

membranes that come in contact with the air and those that come in contact with fluid media? Microscopic evaluation.

- 3) *Hydrogen*. Fluorine can replace hydrogen wherever it is found. What does that mean in terms of structural proteins? What is the three-dimensional affect of fluoride on protein superstructure? How does fluoride bend, twist, contort, stress, distort, or alter the shape of molecules?
- 4) *Calcium*. Calcium is fluorine's 'sweet tooth,' nothing satisfies an insatiable demand as fluorine's as well as calcium—forming an insoluble compound. What is the affect of this 'complex'—does it interfere with vitamin D function—does bone formed without fluoride differ in any observable variable manner from bone formed with fluoride? What does fluoride bone look like with a microscope compared to regular non-fluoride bone?
- 5) *Cancer studies*. What role does fluoride play in breast cancer? It is known that the breast is protective to the offspring in fluoride exposure in milk. Therefore the breast would accumulate fluoride. What is the comparison between breast cancer rates and fluoridation of water? The finding that fluoride interferes with calcium metabolism in all tissues, is observed in studying long bone formation where dysplasia points to a sarcoma mechanism. Several unfortunate molecules were created when fluoride was paired with genetically-active amino acids. Fluorouracil, for example. Despite unprecedented funding for several decades, the cancer 'switch' has not been found. Evidence is mounting that the 'smoking gun' that causes cancer shoots fluoride bullets. This subject needs to be exposed and examined.
- 6) *Bone*. What can we learn from the bone density/bone fracture research? What can we learn about the composition of the bone that fractures? Microscopically—let's take a good look at bone and catalog a few key characteristics. There appears to emerge from the literature the point that although fluoride induces bone growth and density—it does so at the expense of increased fractures. This identifies a role of fluoride when stimulating bone growth—it does so by eating away some calcium (pitting) which then informs the system that some calcium has been taken—deficit induced by fluoride—and then the *osteoblasts* increase their activity which is the response to the negative-feedback of the *osteoclastic* action of fluoride. Research has demonstrated that the end-result of fluoride's bond with calcium is a denser bone, thus higher BMD scores, but the bone is fragile and it shatters like glass, i.e. increased hip and wrist fractures—when you drop it. The literature indicates that fluoride turns bones into stones.
- 7) *Hormone*. What can we learn about the hormone mimicry of F's—do they it amplify, depress, mimic, interfere, or alter? Under what conditions?
- 8) *Immunity*. Calcium is the 'driver' of immunity—what affect does fluoride have on calcium in its immune function and what is fluoride's affect on over-all immune potential, due to the fact that it is known as an enzyme inhibitor?
- 9) *Mitochondria*. Mitochondria are the cellular equivalent to nuclear energy power factories in a suitcase. It is very likely that this is the site of the worst of the damage done by fluoride. It bears note that if fluoride is found to impair mitochondrial function, it is certain that we have altered life and all its forms. If any study demonstrates an impairment to that species mitochondria, it is a universal finding because all of life shares the same mitochondrial mechanism of energy production. We may be enjoying a false sense of security, if we have poisoned mitochondria. This could be catastrophic in scope.
- 10) *Cell membranes*. The microscopic cell membrane study is necessary and should be coupled with uptake and cell-by-product analysis.
- 11) *Tissue culture fluoride concentration study*. Fibroblasts, leukocytes, and stem cells. Grown in increasing fluoride concentration from zero, trace, then 0.05, 0.10, 0.20. up to 2.0 PPM. Measure uptake and excretion from culture media. Measure calcium deltas. See if there is an excretory compensation. Insoluble CaF is formed. Photograph all surfaces possible—cell membrane, nuclear membrane, DNA labeling, look for prolonged responses in tissue quality—thickenings—scar tissue lining vessels. What do we see from looking at this. Corrosion? Pitted, 'rat-bitten' appearances?
- 12) *Receptor sites*. Measure the deltas in receptor site activity under the influence of fluoride. This will be a tremendously helpful tool. It may shed light on the current epidemic of degenerative diseases. What role does fluoride play in the coupling of neurotransmitter substances within the cozy booths of receptor sites?
- 13) *Kidneys*. Immediate investigation is necessary to determine the short- and long-term effects of fluoride exposure to kidney tissues. As a part of the histopathological studies, we need to see what fluoride does to the surfaces of membranes at the contact points, what is the status of the surface of the membrane, the 'tent' of flesh, that is impacted by the stream of blood carrying and concentrating fluoride? Does this membrane display the same type of tissue response we observed in the dogs? The implications of identifying fluoride as a cause of the kidney 'mis-reporting' blood pressure due to membrane thickening or stiffening, as a cause for middle-aged hypertension, are staggering.
- 14) *Heart*. Histopathology examination should be an excellent witness—what do the hearts of non-fluoridated men look like compared to those heavily fluoridated? Does fluoride have an affect on heart rate or conductivity? Can fluoride cause heart attacks electrically by interfering with calcium?

- 15) *Liver*. Again a simple comparison—what do we see? Compare fluoride exposed liver to non-fluoride exposed liver.
- 16) *Circulatory system*. Are leaks, breaks, or ruptures in the human piping of the circulatory system due to the same problems experienced by all three fluoride handling industries—petrochemical, pharmaceutical, and chemical? Should we be aware of fluoride corrosion at work in the human, dogs, and livestock?
- 17) *Reproductive system*. Is male infertility caused by fluorine hijacking the electrons in the electron transport system (ETS) and shutting down the mitochondria riding in the tail of the sperm? Is a fluoride-induced lack of power in sperm a cause of decreasing fertility? Does fluoride interfere with the tubules that form the tracks for the chromosomes to migrate to opposite poles during cell division? Is fluoride accumulation the real agent behind Down's and other mutations, breaks, and deletions?
- 18) *DNA*. Studying the affects of fluoride on DNA in mitotic division must be done. We are likely to observe that fluoride acts to grab hydrogen and calcium at will and pull on them with such a strength that the whole superstructure of the immediate and local environment makes a three-dimensional twist as electrons are pulled in fluoride's direction. The resultant bending and conformational spatial collapse likely wreaks havoc in the highly-conservative DNA environment, creating 'spot-welds' where axis of rotation allowed normal function. Fluoride likely causes the malfunction of the genetic machinery. It is noted that historically, fluoride exposure and the cancer epidemic coincide.
- 19) *Microtubules*. Fluorine's chemical ability to attack microtubules is the basis for prescribing a popular prescription remedy for gout, indomethacin, as an anti-inflammatory. It is expected that fluoride would damage the function of the microtubules which serve like tracks for the chromosome trains as they migrate to opposite poles or sides of the cell. Perhaps rather than just being the result of an aging condition, is it possible that the genetic machinery—the actual physical structures of the cell—rust up? The organelles that depend on each other to hand off information, for example, the G proteins described in this review, are impaired by fluoride.
- 20) *Longevity studies*. Using microscopic evaluation of all tissues exposed to fluoride, which would be all the cells that are subject to water, the long-term effects of fluoride demands investigation. Perhaps, more than the unproductive 'bad' or 'faulty' gene hypothesis, aging is caused or amplified by the physical destruction caused by a lifetime of exposure to fluoride.

Closing comments

The seeds that sprouted into this review were found in the contaminants and particles from smokestack emissions

spewing from coal-fired electricity plants. A global climate change study (*Earth - my new patient*) led to the discovery that coal-fired electricity plants release mercury and fluoride into the atmosphere. Many states, like Colorado, have issued warnings to residents that fish caught in the state's drinking water supply are not safe to eat due to toxins (Denver Post, April 5, 2009).

This paper contains reference to the current and growing finding that between 20–80% of kids display signs of dental fluorosis—over-exposure to fluoride. From the beginning, the ADA has argued that fluoride-stained teeth is a 'cosmetic' effect only. The evidence reported in a growing body of worldwide literature is producing an alarming rebuttal to this baseless and completely-disproven assertion.

Fluoride is a poison and it must become the prime suspect, a potential new vector in a wide range of treatment-resistant diseases. Since the 1980s the disease vector has shifted from infection to toxicity. After reviewing the now-populous field of data that has had more than 80 years or so to mature, the initial and solely-stated reason for adding fluoride to the public water supply (dental caries) is not found within the body of that literature.

To the contrary, it has been observed worldwide that the action of fluoride on all living tissue is always damaging and harmful. If we were to consider only fluoride's affinity for calcium, we would understand fluoride's far-reaching ability to cause damage to cells, organs, glands, and tissues. Additional harm from fluoride's ability to mimic hormones, it's protein-bending effect on genetic materials (which is likely its mechanism as a mutagen and carcinogen), arthritic change in the skeleton, decreased IQ, impaired immunity, and Alzheimer's implication provide such significant evidence that the question is begged—how long will it stay in the water?

How much more of a threat could the public-water consumer be exposed to—terrorist or otherwise—than the known harm that arrives today from the tap and showerhead in our public water? Our life-sustaining water is now contaminated with an industrial-waste which is substituted for an untested sodium fluoride. Should fluoride, in any form, continue to remain in the public water supply, in a time of heightened fiscal responsibility, another *positive* reason than dental caries prevention in children must be found to justify continuing what is proven to be an ineffective and health-damaging expenditure of public funds. At present, it is clear, from nearly 100 years of research, that a positive beneficial reason does not exist and cannot be found. Fluoride is a non-biological chemical.

Fluoride is a poison and it must become the prime suspect in a wide range of diseases, dysfunctions, stiffness, weakness, and pain. After reviewing this expanding field of data, gathered from a generation of perspective, adding fluoride to the public water supply is neither justified nor supported by the body of reported research on the subject. Why fluoride remains in the public water supply, since 1999, when it was learned that the systemic pathway of fluoride had been disproven, requires examination. Once the action of fluoride is known to be topical, i.e., there is no reason to swallow

fluoride— the reason for adding it to public water supply dissolves. Another reason than dental caries in children must be found for the continued health-challenging, and knowingly ineffective expenditure of public funds.

Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content, writing, and editing of this review.

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