

Fluoride: Benefits And Risks of Exposure

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I. INTRODUCTION

This report describes the benefits to dental health of exposure to fluorides and the toxicologic effects of fluorides based on the relevant scientific literature published through September 1988. In general, original reports were used for evaluation of results between 1980 and 1988, and review articles were used for results published prior to 1980. This report is confined to effects of inorganic fluorides. Throughout this report the term "fluoridation" refers to the addition of fluoride to drinking water supplies.

The halogen fluorine is the most electronegative and one of the most reactive of the elements. Consequently, it does not exist in the elemental state in nature, where in combination it comprises 0.065% of the Earth's uppermost crust. Fluorine forms numerous inorganic salts and also occurs in countless organic compounds, substituting for hydrogen. Fluorides are used in wire and cable insulations, pipe linings, rocket propellants, rodenticides, refrigerants, aerosol propellants, polymers for plastics, in the separation of uranium isotopes, and in the aluminum, beryllium, antimony, superphosphate fertilizer, glass, electronic ceramics, fluorspar, and the brick industries.

In 1945, fluoridation of public water supplies to the optimal concentration of 1 mg/l was initiated in three communities in the U.S. In a census conducted in 1985, it was estimated that 121 million Americans receive supplementary fluoride via this vehicle.¹ There are, however, other sources of fluoride that must be considered in any overall assessment of fluoride intake. Average daily dietary intakes of fluoride are shown in Table 1. Differences in fluoride analytical techniques⁸ and in methods of selecting the foods comprising the diets make comparisons between current food fluoride concentrations and those determined prior to drinking water fluoridation somewhat tenuous. Nevertheless, there are apparently no major increases in current concentrations of fluoride in food associated with water fluoridation.^{2-7,9,10}

Fluorides in the atmosphere arise from fluoride-containing dusts, industrial waste, the burning of coal fires, and volcanic gases. In nonindustrial urban areas, the highest fluoride quantity available for inhalation is approximately 0.04 mg/d but near fluoride-emitting factories this could increase to 4 mg/d.¹¹

Fluoridated toothpastes can provide another major source of fluoride intake, particularly to children. Toothpastes contain 1.0 to 1.5 mg fluoride per gram and based on estimates of an

average ingestion of 0.5 g toothpaste per use for 2- to 5-year-old children, could result in the intake of 0.50 to 0.75 mg fluoride per use.¹¹ For 7 to 13 year olds the estimate was 0.4 to 1.2 mg fluoride per use.¹² These recent estimates are higher than in earlier reports.¹³ Fluoride-containing mouthwash could contribute 0.2 to 0.4 mg fluoride per use.¹² Fluoride tablets and topical gels represent additional sources of fluoride exposures.

II. PHARMACOKINETICS

Fluoride is absorbed through the gastrointestinal and respiratory tracts. Dermal absorption is negligible except in cases of hydrofluoric acid burns.¹⁴ Fluoride crosses the placenta and is absorbed by the fetus.¹⁴ At birth, infant serum fluoride levels are approximately 75% of maternal levels.¹⁵

Soluble fluoride compounds are rapidly and almost completely (>90 to 95%) absorbed across the gastrointestinal tract.^{14,15} Peak serum levels occur within 30 min of ingestion on a fasting stomach. When fluoride is ingested with food or complexed with certain inorganic salts (e.g., calcium, phosphate, magnesium, aluminum), the degree and rate of absorption are decreased.

Fluoride is rapidly distributed in plasma and deposited in bone and other calcified tissues such as teeth. Approximately 50% of the daily fluoride intake is deposited in calcified tissue.¹⁴ Skeletal fluoride accounts for approximately 99% of the body burden, with the remainder distributed between blood and soft tissues. The half-life of fluoride in plasma ranges from 2 to 9 h, depending on the dose level and is several years in bone.^{14,16,17}

Fluoride concentrations in plasma and bone are highly variable and increase with fluoride intake and age.^{14,18} Mean plasma ionic fluoride concentrations among persons living in communities with nonfluoridated drinking water supplies (<0.3 mg/l in drinking water) range from 0.004 to 0.02 mg/l. In optimally fluoridated communities (0.7 to 1.2 mg/l), they range from about 0.02 to 0.04 mg/l.^{18,19} Peak plasma fluoride concentrations vary depending on the fluoride dose and pattern of exposure. Following a single oral intake of 0, 1.5, 3, 6, or 10 mg fluoride, peak plasma fluoride levels were 0.01, 0.06, 0.13, 0.22, and 0.42 mg/l, respectively.²⁰ Typical levels in adult bone vary between 500 and 4000 mg/kg in bone ash.^{15,21,22}

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Table 1
Average Daily Dietary Fluoride Intakes in the U.S.

Population group	Period	Source		Ref.
		Food only Fluoride per day (mg)	Food, drinking water and beverages Fluoride per day (mg)	
15- to 19-year-old males, throughout U.S.	1975—1982	0.33 ^a (0.21—0.72) ^c	1.43 ^{a,b}	2
Infants, throughout U.S.	1977—1982	0.17 ^a (0.049—0.257) ^c	0.35 ^{a,b}	3
Toddlers, throughout U.S.	1977—1982	0.16 ^a (0.107—0.314) ^c	0.46 ^{a,b}	3
Infants, New York State	1987	0.15 ^a	0.32 ^{a,b}	4
Adults, throughout U.S.	Early 1940s		0.25—0.30	5
Adults, Minnesota General Hospital	1942	0.27—0.32 ^c		6
Adults	1942		0.45	7

^a Based on market basket food collections.

^b The average dietary intake from food, water, and beverages is dependent on the ratio of communities with and without fluoridated water, used in the study.

^c Range.

Fluoride is predominantly excreted by the kidneys.^{14,15} Approximately 40 to 60% of the daily fluoride dose is excreted in the urine with an elimination half-life of about 5 h.^{14,17} Fluoride is also eliminated in sweat, breast milk, and saliva.¹⁴

III. BENEFITS OF FLUORIDE

This section reviews studies describing the relationship between dental caries prevalence and fluoridated drinking water, as well as studies reporting decreases in dental caries in non-fluoridated areas. A discussion of methodologic issues relating to these studies is included.

A. Fluoride and Dental Caries

The cosmetic effects (fluorosis or dental mottling) of fluoride-containing water were first observed in the early 1900s. The presence of this then-unidentified agent in drinking water was also suspected of having a protective effect on dental health. It was not until the 1940s that a relationship between naturally occurring fluoride in drinking water and the prevalence of dental caries was demonstrated by U.S. Public Health Service researchers.^{23,24} These investigations indicated reductions of 50 to 60% in caries prevalence among children who drank water with natural fluoride levels of 1.0 mg/l or greater compared with children residing in communities with less than 0.3 mg/l. The Report of the Working Party on Fluorides in the Control of Dental Caries¹³ indicates several studies that have demonstrated that exposure to fluoridated water in adolescence provides caries inhibition into adulthood. The studies by Dean et al. led to the adoption of 1 mg fluoride per liter as an optimal

level for drinking water supplies based on substantial reductions in dental caries without objectionable levels of dental fluorosis.

Murray and Rugg-Gunn²⁵ have summarized published reports of 95 fluoridation projects initiated in 20 counties between 1945 and 1972. A total of 128 studies are reviewed because reports specific to deciduous and permanent teeth are presented separately. Overall reductions in caries prevalence in permanent teeth ranged from 29 to 85%, with a mean decrease of 55.6%.²⁵ In studies of deciduous teeth, decreases in dental caries prevalence ranged from 20 to 76%, with a mean decrease of 48.9%.²⁵ Findings from these investigations are summarized in Figure 1.

The 1979 to 1980 National Dental Caries Survey examined U.S. children ages 5 to 17 years and found 33% fewer carious surfaces among children continuously exposed to fluoridated water (1 mg/l) than among children without exposure to fluoridated water, as reported in an abstract (3.7 and 5.5 DMF [number of decayed, missing, and filled teeth], respectively).²⁶ Children in Birmingham, England, a fluoridated community, experienced a 54% reduction in caries between 1970 and 1980 compared with a 32% reduction observed among children in a comparable nonfluoridated community.²⁷ Among 17-year-old naval recruits (n = 1332) in the U.K., who had resided in one area since birth, a 20% difference in caries prevalence has been reported among recruits living in areas with low (0.1 mg/l) fluoride levels compared with recruits residing in areas with optimal fluoride levels (1.0 mg/l).²⁸ A 40% difference in DMF scores has been reported among 14-year-old children residing in fluoridated Bolton (1.0 mg/l) and nonfluoridated

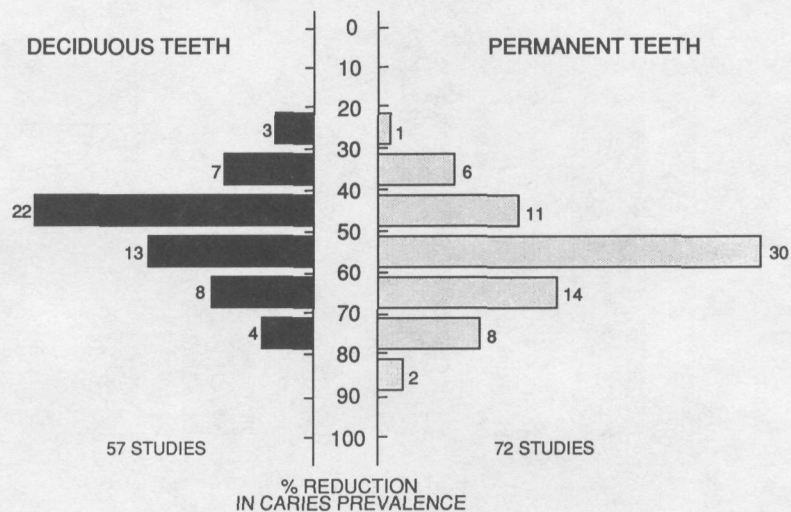


FIGURE 1. A summary of the percent reduction in dental caries based on a review of studies investigating the effectiveness of artificial fluoridation of drinking water. (Data adapted from Murray, J. J. and Rugg-Gunn, A. J., *Fluorides in Caries Prevention*, 2nd ed., Derrick, D. D., Ed., Wright-PSG, Boston, 1982.)

South Birmingham (<0.1 mg/l) in the U.K.,²⁹ significant differences were apparent in the mean number of decayed teeth and filled teeth in these areas.

A study of Michigan schoolchildren (ages 6 to 12) considered dental caries, fluorosis, and fluoride exposure. Of the children in areas where fluoride was undetectable in the drinking water, 55% were caries free, and 12% had mild dental fluorosis compared with 74% caries-free children in areas with fluoride at 1.0 mg/l, where 49% had mild dental fluorosis.³⁰ Although a standardized protocol is used in the examination of fluorosis, final determination of fluorosis prevalence and severity is based on subjective assessments by dental examiners. A significant relationship between the caries-free percent of the population and increasing fluoride levels was also observed in this study. Findings in this study suggest that children in fluoridated and nonfluoridated areas seem to be ingesting similar amounts of fluoride from fluoride-containing dental products. However, the authors determined that the fluoride concentration in drinking water defined levels of caries and dental fluorosis in their study.³⁰

Kumar et al.³¹ have recently completed a study that examined trends in the prevalence of dental fluorosis and caries in Newburgh and Kingston, two New York State cities involved in early studies evaluating the efficacy of fluoridation of water supplies. Water in Newburgh has been fluoridated at 1 mg/l since 1945, except for the 3-year period 1978 to 1981, while Kingston has maintained a natural fluoride level of 0.3 mg/l. Consistent with earlier reports from Texas and Illinois, no changes in the prevalence of dental fluorosis were noted among Newburgh children between 1955 and 1986. Among children residing in Kingston, dental fluorosis increased during the same period. While increased fluorosis in nonfluoridated areas has

been reported previously, the authors attributed this observation of increased fluorosis to the greater use of fluoride supplements in the Kingston area, where 31% of the children reported daily use of fluoride tablets/drops compared with 5% of children reporting daily use of fluoride supplements in Newburgh.³¹

Based on three dental surveys conducted in Kingston and Newburgh, the age- and race-adjusted prevalence of dental caries among children ages 7 to 14 decreased in both fluoridated and nonfluoridated areas during the last 40 years.³¹ Between 1944—1946 and 1954—1955, age- and race-adjusted caries prevalence (mean DMF) in Newburgh decreased from 4.7 to 2.9, while caries prevalence in Kingston increased from 4.7 to 5.5 over the same period. From 1954 to 1955 through 1986, the mean caries prevalence in Newburgh demonstrated further decline to 1.5, while mean caries prevalence in Kingston demonstrated a greater rate of decline to 2.0.³¹ Changes in caries prevalence in the Kingston and Newburgh areas are presented in Figure 2.

Studies of communities where fluoridation has been terminated provide support for the benefits of fluoridation, such as those undertaken by Stephen et al.³² in Scotland. The study area was fluoridated from 1969 to 1979; fluoridation was discontinued in 1980. By 1984, DMF scores among children 5 to 6 years old had increased almost 40% and 10% fewer children were caries free relative to results determined in 1979.

The effects of withdrawal of fluoride from drinking water were also studied in Antigo, Wisconsin, a community that initiated fluoridation in 1949, terminated fluoridation in 1960, then resumed fluoridation in 1965. Only children who reported continuous residence in this area were included. Between 1960 and 1966, kindergarten children demonstrated a 112% increase in caries prevalence. Caries prevalence also increased 233%

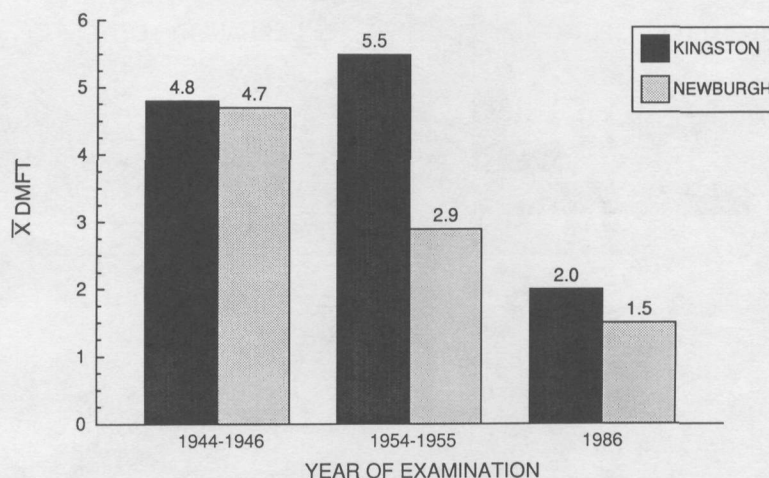


FIGURE 2. Age- and race-adjusted dental caries prevalence (DMFT) for 7- to 14-year-old children in Newburgh, New York, which has had fluoridated drinking water from 1945, and Kingston, New York, which has not had its drinking water fluoridated. (Data adapted from Kumar, J. V., Green, E. L., Wallace, W., and Carnahan, T., *Am. J. Public Health*, 1988.)

among second graders, 70% among fourth graders, and 91% among sixth graders during the same period.³³ The proportion of caries-free children decreased over 50% at all grade levels between 1960 and 1966.

A recent study by Attwood and Blinkhorn³⁴ compared the prevalence of dental caries in two communities in Scotland. The town of Stranraer had a fluoridated water supply until 1983, while Annan, a comparable community, had "negligible" levels of fluoride. Caries prevalence among children in Annan showed a significant decrease of 16% between 1980 and 1986; however, children in Stranraer did not demonstrate any change in caries prevalence.³⁴ The authors concluded that these data provided evidence of a detrimental effect from the termination of water fluoridation 3 years earlier.³⁴

The reports summarized above indicate that fluoridation of drinking water is associated with decreased dental caries. However, there are reports that in nonfluoridated areas similar decreases have been observed. Diesendorf³⁵ has noted 23 published studies that report sizable decreases in dental caries in nonfluoridated areas during the past 30 years. Decreased caries prevalence has been observed in several parts of the U.S. with nonfluoridated water supplies.^{36,37} Reductions in caries prevalence of 35% and 49% were observed among British school children (age 12) in the nonfluoridated communities of Somerset and Devon, respectively, over 10- and 15-year periods.³⁸ These investigators also reported a 45% decrease in caries prevalence among 5 year olds in nonfluoridated Dudley, England, between 1970 and 1980.³⁸ Examination of 12-year-old children in Shropshire, England, a nonfluoridated community, revealed a 32% decrease in caries prevalence between 1970 and 1980.³⁹ Decreases in caries prevalence have also been

reported among Scandinavian children, where water supplies are not fluoridated.^{40,41} In this report, the decrease was hypothesized to have resulted from the use of fluoride rinses and toothpastes. Reductions in caries prevalence observed in nonfluoridated areas are summarized in Figure 3.

Many studies have attempted to explain decreases in dental caries prevalence observed in nonfluoridated areas. Possible reasons for observed declines in the prevalence of dental caries during the past 10 to 20 years have included the decreased consumption of refined sugar, improved availability and utilization of dental health services, increased uses of fluoride-containing dental care products, and changes in oral flora resulting from the extensive use of a wide spectrum of antibiotics, improvements in oral hygiene, and increased awareness of dental health.^{35,37,42} However, no change in per capita consumption of sugar in the U.S. has been noted during the last 10 years,⁴³ suggesting that the caries decline in nonfluoridated areas is due to factors other than changes in sugar consumption. Increased usage of other fluoride-containing products may partially explain declines in caries prevalence in these areas;⁴³ however, other factors, as yet unidentified, may be operating.

Two published studies have used a longitudinal design to evaluate the impact of fluoride sources on dental health. Fergusson and Horwood⁴⁴ investigated the relationship between sources of fluoride, social background, and dental health by following a cohort of children (n = 1265) in New Zealand from birth through age 7 years. Annual examinations were performed and information on exposure to fluoride, use of fluoride tablets, and social background of the family was collected for all participants in an attempt to measure exposure to fluoride from a number of sources over a period of years

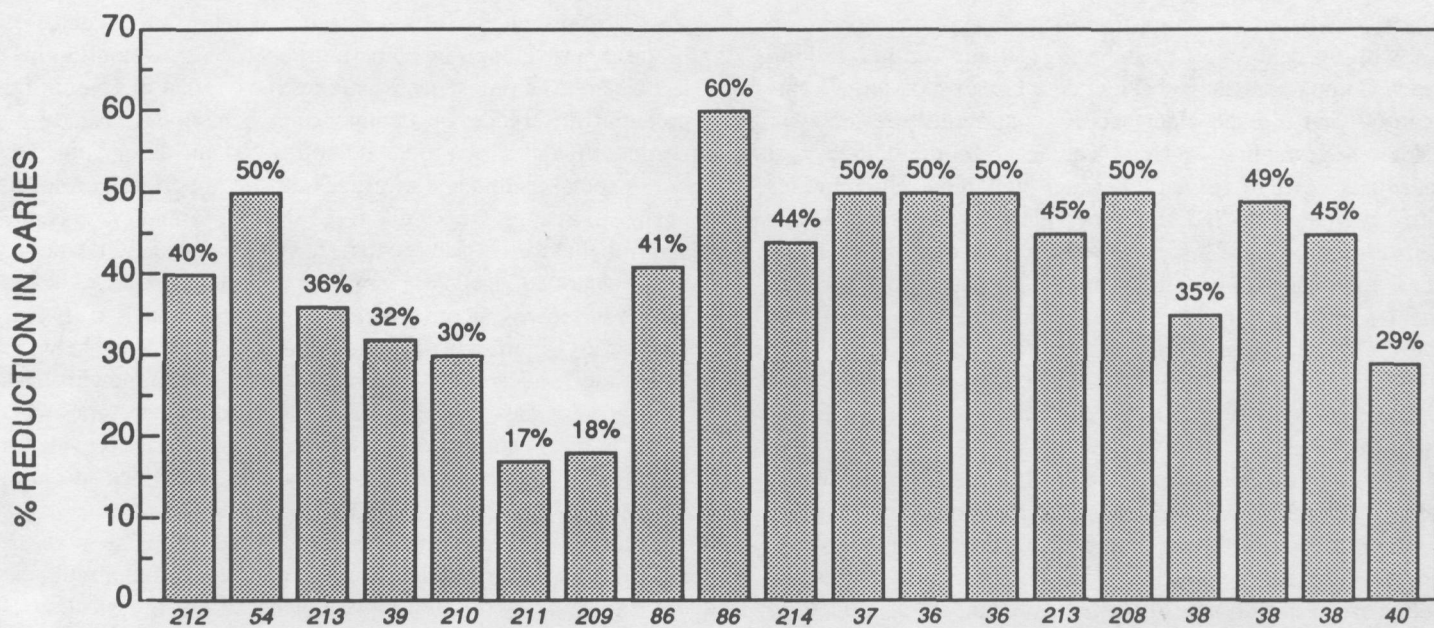


FIGURE 3. Reductions in dental caries among children living in areas with nonfluoridated drinking water. References for the data are provided below the data bars.

and the effects of this exposure. Univariate analysis revealed an inverse relationship between DMF scores and maternal education and family socioeconomic status.⁴⁴ However, in a regression model, these social factors explained only 4% of the variability in DMF scores. A log-linear model demonstrated significant inverse associations between DMF scores and use of fluoride tablets, social background, and residence in a fluoridated community. Additionally, among children who did not report use of fluoride tablets, an inverse relationship was observed between DMF scores and years of exposure to fluoridated water.⁴⁴

Klein et al.⁴⁵ also employed a longitudinal design to evaluate the cost and effectiveness of school-based programs for preventive dental care. Five fluoridated and five nonfluoridated communities throughout the U.S. were selected to evaluate several preventive dental care procedures during a 5-year period. Study sites varied in level of urbanization, socioeconomic status, and proportion of minority population. While 20,000 students were initially enrolled, only 48% received both baseline and final examinations. Of the procedures examined, occlusal sealants were observed to be most effective, reducing DMF scores among first and second graders by 1.33 in non-fluoridated areas and 0.96 in fluoridated areas during the 4-year study period.⁴⁵ School-based procedures such as weekly fluoride mouth rinsing, daily fluoride tablets, biannual fluoride paste/gel applications, dental health lessons, and biweekly brushing and flossing did not produce significant reductions in decay.⁴⁵ (The independent effect of fluoridated drinking water on caries prevalence was not determined in this study; however,

lower caries prevalence was noted in fluoridated areas prior to the initiation of treatments.)

Root surface caries are more frequent during the later years of life, and their importance as a dental health outcome among adults is increasing as the general population ages and as persons retain their teeth for longer periods.⁴⁶ Fluoridated drinking water has been reported to reduce the prevalence of root caries among adults. Stamm and Banting⁴⁷ investigated root surface caries among lifelong adult residents of two communities in Ontario, Canada, and reported (in a preliminary unrefereed report) 52% fewer carious root surface lesions among persons in the fluoridated community. Lifelong residents of naturally fluoridated Stratford (1.6 mg/l) had an average of 0.64 root surface caries per person (average age 40.2 years) compared with lifelong residents of nonfluoridated Woodstock, who exhibited an average of 1.36 root surface caries per person (average age 42.8 years).⁴⁷ The relationship between natural levels of fluoride in drinking water and root caries has also been explored by Burt et al.⁴⁸ This study compared the prevalence of root surface caries among lifelong adult residents (ages 27 to 50 years) of two rural New Mexico communities with different natural fluoride levels. Root surface caries prevalence in Deming (0.7 mg F per liter) was 23.5% (mean age 39.8 years) compared with a 7.3% prevalence of root surface caries in Lordsburg (3.5 mg F per liter, mean age 43.2 years). The mean number of root caries lesions was significantly greater in Deming (0.69 lesions per person examined) compared with Lordsburg (0.08 lesions per person examined). Questions remain regarding the generality of these results since the com-

parison was based on a high-fluoride area (Lordsburg) and an area with optimal levels of fluoride (Deming) in the drinking water. Comparisons have been undertaken of root surface caries in 60 year old and older people, continuously resident for at least 8 years in two New York State communities with "adequate" (1.0 to 1.2 mg F per liter) and in two communities with "deficient" (<0.1 mg F per liter) levels of fluoride in their drinking water.⁴⁹ Among persons with exposed root surfaces, the proportion with carious and/or filled root surfaces was 7.8% in the nonfluoridated communities compared with 1.8% in the fluoridated communities.⁴⁹

B. Exposure to Fluoride Levels Exceeding 1 mg/l in Drinking Water

Driscoll et al.⁵⁰ have reported further reductions in caries prevalence of 37% and 55% among children receiving drinking water with fluoride levels of 2.0 and 3.0 mg/l, respectively, relative to levels of 1.0 mg/l; however, at 4.0 mg/l, the protective effect of fluoride is diminished. Comparable reductions in caries prevalence, as a function of fluoride concentrations in drinking water, were recently reported by Heifetz et al.⁵¹ Compared with children with no clinically apparent fluorosis, New York State children with very mild to moderate dental fluorosis exhibited reductions of 41 to 54% in caries prevalence.³¹

Reductions in the prevalence of dental caries were observed at fluoride levels two, three, and four times the recommended level. However, levels of 3.0 mg/l produced the greatest reduction in caries prevalence. Higher levels of fluoride did not result in further reductions in caries prevalence. At increased fluoride levels, the severity of mottled enamel and dental fluorosis is more pronounced. A fluoride concentration in excess of 3 mg/l is thought to result in the development of defective tooth enamel, rendering the tooth surface more susceptible to decay.⁵²

C. Other Benefits of Fluoride

Based on the observation that excess amounts of fluoride produce denser bones, fluoride has been suggested as a therapeutic agent in the treatment of osteoporosis.^{13,14,53} It is thought that fluoride, in conjunction with calcium, stimulates osteoblastic activity; fluoride, integrated into the bone matrix as fluorapatite, increases the hardness of bones. Further study is needed to evaluate the efficacy of this treatment.

D. Methodologic Issues in Studies of Fluoride and Fluoridation

Studies investigating the effect of fluoridation on dental caries suffer from several methodologic limitations. Most studies published to date have relied on ecologic designs and lack precise measures of exposures to fluoridated drinking water on an individual basis. Exposure status is based on fluoridation characteristics of a town or water district. As an example, this

classification scheme is used in studies demonstrating decreases in caries prevalence in both fluoridated^{23,24} and nonfluoridated⁵⁴⁻⁵⁶ areas. In most cases, studies have failed to account for potential differences in dental health behaviors. A study by Fergusson and Horwood⁴⁴ demonstrated an association between social factors and awareness of the importance of dental health, indicating the need to request this information on dental health behaviors in future studies. With widespread decreases in caries prevalence and overall improvements in dental health behaviors, it will become increasingly more difficult to observe statistically significant differences in caries prevalence between fluoridated and nonfluoridated areas. Study designs will have to reflect increased sample sizes, lengthened observations periods, or use of subpopulations that have high caries prevalence to increase the ability to observe a true difference in caries prevalence.¹⁵

Similarly, all studies, whether they refute or support the fluoride-dental caries relationship, experience problems of generalizability. These studies are not based on the selection of random samples of participants, representative of the general population, but instead recruit volunteers for participation.⁵⁷ While the investigator(s) recognize these limitations, it is important to emphasize them when drawing conclusions from this research.

Studies of caries prevalence have been criticized for being inappropriate to support trend analysis, failing to follow standardized protocols, and not including representative samples of the population.⁵⁸ Burt and Beltran⁵⁸ also suggest caution regarding possible confounding of results due to misclassification of residence, misclassification of fluoride histories, and use of a proxy measure to characterize the caries experience of the study population. These cautions apply equally to studies supporting and refuting the anticariostatic effects of fluoride in drinking water. A longitudinal study has indicated the importance of obtaining accurate information on residence and on exposures to other sources of fluoride.⁴⁴

Studies assessing the effect of fluoridation on the prevalence of dental caries need to consider a number of issues. Frequent reliance on group-based data for exposure to fluoride fails to account for individual differences in susceptibility to tooth decay or behaviors likely to influence decay.⁵⁷ We were able to identify only one study that prospectively measured exposure to a variety of fluoride sources on an individual basis.⁴⁴ Dental health-care practices are likely to influence exposure to sources of fluoride exposure other than drinking water. For example, fluoride-containing dentrifices captured only 67% of the U.S. market in 1967, but their market share had increased to 94% by 1984.⁵⁹ Few studies have evaluated the impact of dental health-care practices and their independent relationship to caries prevalence.

Studies have often relied on the use of subjective measures (diagnostic standards) of the dependent variable precluding interstudy comparisons.⁵⁷ Incipient carious lesions may be dif-

difficult to detect among the young. Among adults, missing teeth may have been lost due to reasons other than decay. On the other hand, some variation in clinical diagnostic measures is expected; however, the DMF examination represents a standardized and reproducible protocol.

Population mobility has also not been taken into account in most studies.^{23,24,54,55,60} Grembowski⁶¹ has indicated that population mobility can result in random measurement error with bias toward zero, i.e., failing to detect an effect. Studies completed to date have also not adequately accounted for the heavy weighting of exposure to fluoride through drinking water. This source of fluoride may account for only a portion of total fluoride intake, suggesting that exposures to other fluoride sources need to be quantified and related to studies of caries prevalence. It will be difficult to assess the cariostatic effect of fluoride exposures in drinking water independent of fluoride exposure from dental-care products due to the widespread use of fluoride-containing dentrifices, mouth rinses, fluoride tablets, and dental sealants.

As examples of general methodologic problems with many of these studies, the strengths and limitations of two studies will be briefly highlighted. These two studies have been selected only to provide illustrations of several of the methodologic issues discussed previously.

Ast et al.⁶² have summarized the findings of the Kingston-Newburgh study 10 years after this investigation was initiated. This study reported reductions in dental caries prevalence of 58% among Newburgh children continuously exposed to fluoridated water (1 mg/l). Reductions in caries prevalence of 41 to 52% were also reported among Newburgh children who were not exposed to fluoridated water their entire lives. Comparisons were made with children of similar ages residing in Kingston (0.3 mg fluoride per liter). This study used a single examiner to conduct oral examinations of every other child between ages 6 and 12 in these two cities. Only lifetime residents were included to control for the effects of population mobility. Bitewing radiographs were examined blindly. While other supplemental sources of fluoride were nonexistent, a limitation of this study included the lack of individual measures of fluoride exposure. No attempt was made to determine access to dental care. The applicability of findings to other communities can also be questioned.

Glass³⁶ reported decreases in caries prevalence in two Massachusetts towns over a period of 20 years. Caries prevalence decreased 50% in both Dedham (1958 to 1974) and Norwood (1958 to 1978). Both towns used nonfluoridated water supplies (0.1 mg/l) during the study periods. The two towns were middle class, residential communities, and the results are only applicable to similar areas. All examinations were completed by the same clinician using a standardized protocol; bitewing radiographs were obtained to confirm results of the clinical examination. An ecologic design was used in this study. Exposures to other sources of fluoride and changes in dental health prac-

tices during the study period were not evaluated. Reported decreases in caries prevalence were based on time trend analyses and did not involve comparison with similar communities. In addition, the study relied on a rather small sample of the population in each area; however, the results are consistent for both study areas. Thus, strengths and limitations have been noted in both of the studies, which have been highlighted.

E. Summary

Ecological studies conducted in the 1940s and 1950s reported a substantial decrease in dental caries prevalence among children residing in areas with fluoridated water supplies (1.0 mg/l) when compared with areas with less than optimal fluoride levels in drinking water (<0.3 mg/l). These early studies were able to assess the impact of fluoridated water on caries prevalence since supplemental sources of fluoride other than water were nonexistent. There are also reports that termination of fluoridation is followed by increases in caries prevalence in young children. Together, these studies indicate that fluoride in drinking water is beneficial to dental health.

However, recent studies have reported declines in caries prevalence in nonfluoridated areas that are comparable in magnitude to declines noted in fluoridated areas. While these estimates of caries decreases in nonfluoridated areas appear accurate, conclusions cannot be drawn from these studies concerning the independent effects of fluoridated drinking water on caries prevalence since other possible sources of fluoride exposure were not measured. Fluoride sources, other than in drinking water, may provide a level of caries protection similar to fluoridated drinking water. A longitudinal study conducted in New Zealand, which followed a cohort of children from birth through age seven, found that caries prevalence demonstrated an inverse relationship with use of fluoride tablets, social background, and length of residence in a community with fluoridated water. This study highlighted the importance of measuring sources of exposure to fluoride and the duration of these exposures.

While there are no published studies that clearly explain reasons for caries declines in nonfluoridated areas, several factors may be important. Over the last 30 to 40 years, access to dental care and knowledge of dental hygiene have improved. A heightened awareness of dental hygiene and of the beneficial effects of fluoride-containing dental-care products has occurred as a result of studies demonstrating the efficacy of fluoride. Exposure to various sources of fluoride through fluoridated toothpastes, fluoridated mouth rinses, fluoride tablets, and fluoride-containing dental sealants has increased the availability of fluoride. As a result, the effects of fluoride exposure cannot be accurately assessed based solely on the fluoride content of drinking water in an area. The preponderance of evidence indicates that fluoride in drinking water has a beneficial effect on dental health. Due to the ubiquitous nature of exposures to fluoride sources other than drinking water, firm

conclusions cannot be drawn regarding the independent effect of fluoride in drinking water and caries prevalence using an ecologic study design.

IV. ADVERSE EFFECTS OF FLUORIDE

A. Acute Toxicity

Symptoms of acute oral fluoride intoxication in humans include severe nausea, vomiting, hypersalivation, abdominal pain, and diarrhea. In severe or fatal cases, these symptoms are followed by convulsions, cardiac arrhythmias, and coma.⁶³⁻⁶⁵ Acute toxic doses range from 1 to 5 mg/kg;^{14,64,65} doses exceeding 15 to 30 mg/kg may be fatal.⁶⁴ Acute effects in experimental animals are similar to those observed in humans. Acute oral LD₅₀ values for fluoride compounds in laboratory animals range from 20 to 100 mg/kg.¹⁴

A probable toxic dose of 5 mg fluoride per kilogram can be reached in a 10 kg, 1-year-old child after ingestion of approximately 50 1-mg fluoride tablets, 50 g of 1000 ppm-fluoridated toothpaste, or 50 ml of 0.2% sodium fluoride rinse, or 0.4% stannous fluoride rinse or gel.⁶⁴ Ingestion of approximately twice these amounts can cause toxicity in a 5-year-old child.⁶⁴ Mild gastrointestinal symptoms of acute intoxication may occur at doses as low as 1 mg fluoride per kilogram or about one fifth of the probable toxic dose.⁶⁵ Fluoride rinses are not recommended for use in children under 6 years old, since young children usually have inadequate control of their swallowing reflexes.^{64,65}

B. Chronic Toxicity

Several comprehensive reviews on the health effects associated with low-level fluoride exposure are available.^{14,66-70} Chronic exposure to excessive fluoride is known to cause dental fluorosis (discoloration and mottling of teeth) and skeletal fluorosis in humans.^{14,67,70} Other effects, including hypersensitivity reactions,^{71,72} renal insufficiency,^{73,74} and a possible association with repetitive strain injury,⁷⁵ have also been reported. Reports on birth defects^{76,77} and cancer⁷⁸ are also discussed (see the reproductive/developmental effects and carcinogenicity sections).

1. Dental Fluorosis

Dental fluorosis results when excessive amounts of fluoride are ingested during the years of tooth formation.¹⁵ Dental fluorosis is characterized by lusterless, opaque white patches in the enamel, which may become stained yellow to dark brown, and in severe forms cause marked pitting and brittleness of teeth. The severity of dental fluorosis is usually ranked according to Dean's classification index⁷⁹ as questionable, very mild, mild, moderate, or severe. Recently, the tooth surface index of fluorosis (TSIF) has been used to assess the severity and prevalence of dental fluorosis.⁸⁰ In the questionable to mild categories, teeth have small white opaque areas covering less

than 50% of the enamel surface. Mild forms of fluorosis are not readily observable by the general public and often resemble endogenous nonfluoride enamel opacities.⁷⁰ Objectionable fluorosis is usually defined as moderate or severe fluorosis demonstrating observable staining and/or pitting of teeth.^{81,82}

The prevalence and severity of dental fluorosis increase with increasing fluoride concentrations in drinking water. The prevalence of objectionable fluorosis is less than 1% at water fluoride levels below 0.3 mg/l,⁸²⁻⁸⁴ approximately 1 to 2% at 1 mg/l,⁸²⁻⁸⁴ ranges from 3 to 15% at 1.8 to 2.3 mg/l,^{50,51,82} and ranges from 7 to 33% at 2.4 to 4.1 mg/l. Severe fluorosis is only consistently observed at levels exceeding 2.5 mg/l.⁶⁷ Objectionable fluorosis has also been reported following daily ingestion of fluoride supplements containing 0.5 mg fluoride during the first 2 years of life, but has not been observed with daily supplements of 0.25 mg fluoride.⁶³

Several studies have indicated that the prevalence of mild forms of fluorosis in the U.S. has increased in recent years in both optimally fluoridated and nonfluoridated communities compared with original prevalence scores reported by Dean in the 1940s for children exposed to similar levels of natural fluoride in their water supply.^{30,83,85} The prevalence of all categories of fluorosis reported in recent studies conducted in New York,⁸³ Texas,⁸⁵ and Michigan³⁰ ranges from 26 to 51% in optimally fluoridated communities (0.7 to 1.2 mg/l) and 2.4 to 12% in nonfluoridated areas (<0.3 mg/l). These values are higher than those previously reported in Dean's studies on children exposed to naturally fluoridated and nonfluoridated water in Illinois (i.e., 12 to 33% fluorosis in areas with 0.9 to 1.2 mg/l fluoride and 0 to 2.2% fluorosis in areas with <0.3 mg/l fluoride in water). Driscoll and co-workers^{50,80} recently examined the prevalence of dental fluorosis among children living in optimally fluoridated (1 mg/l) and nonfluoridated (<0.3 mg/l) communities in Illinois and Iowa and found that the prevalence of fluorosis (15 and 2.9% in fluoridated and nonfluoridated areas, respectively) had not increased over time. However, in the optimally fluoridated area, a higher prevalence of fluorosis was observed in younger (8 to 10 years old) children than in older (13 to 16 years old) children. In all of these studies, the overall severity of fluorosis, as assessed by the community fluorosis index, has not increased.⁸³ Leverett⁸⁶ postulated that increased exposure to fluoride from sources other than fluoridated water, such as foods processed in fluoridated water, fluoride dentifrices, and fluoride supplements, may account for the apparent increased prevalence of fluorosis. However, Heifetz and co-workers⁵¹ suggest that this phenomenon may be transitory due to the enactment of cautionary measures in the late 1970s, which removed fluoride from commercially processed baby foods and lowered the recommended fluoride supplement level for children under the age of 2.

2. Skeletal Fluorosis

Skeletal fluorosis is a chronic metabolic bone and joint dis-

ease caused by chronic exposure to high doses of fluoride.^{14,87} Skeletal fluorosis has several stages: two preclinical asymptomatic stages characterized by slight radiographically detectable increases in bone mass; an early symptomatic stage characterized by sporadic pain and stiffness of joints and osteosclerosis of the pelvis and vertebral column; a second clinical phase associated with chronic joint pain, arthritic symptoms, slight calcification of ligaments, and increased osteosclerosis of cancellous bones, sometimes accompanied by osteoporosis of long bones; and crippling skeletal fluorosis characterized by marked limitation of joint movements, considerable calcification of ligaments, crippling deformities of the spine and major joints, muscle wasting, and neurological defects associated with compression of the spinal cord.

Epidemiological studies conducted in the U.S. have not detected radiographic changes in bone density in persons drinking water containing less than 4 mg fluoride per liter.⁸⁸⁻⁹¹ No evidence of radiographic changes in bone or effects on skeletal maturation were seen in children exposed to 1.2 mg/l of fluoride in water for 10 years⁸⁹ or living since birth in areas of Texas with naturally high levels of fluoride (3.3 to 6.2 mg/l) in water supplies⁹⁰ compared with children living in nonfluoridated (<0.2 mg/l) communities. No statistically significant differences in bone mass (by single photon absorptiometry) were observed in women exposed to 4 mg/l of fluoride in their water vs. those exposed to 1 mg/l.⁹¹ A statistically significant higher incidence of bone fractures was reported among older (55 to 80 years old), but not younger (20 to 35 years old), women residing in the high-fluoride area.⁹¹ However, frequency of bone fracture among older women did not correlate with length of residence in the high-fluoride community or with relative extents of fluoride exposure.⁹¹ Stevenson and Watson⁸⁸ examined 170,000 spinal and pelvic X-rays taken over a 10-year period of persons living in Texas and Oklahoma. No evidence of fluoride osteosclerosis was detected in X-rays of persons with less than 4 mg/l of fluoride in their water supply, whereas 23 cases of osteosclerosis were detected in X-rays of persons exposed to 4 to 8 mg/l of fluoride. Similarly, radiographically detected osteosclerosis was reported in 10 to 15% of individuals exposed for an average of 37 years to water containing 8 mg/l of fluoride in Bartlett, Texas.⁹² However, clinical symptoms of skeletal fluorosis were not found in either of these studies. Crippling skeletal fluorosis is associated with chronic fluoride intakes of 20 to 80 mg/d for 10 to 20 years.^{14,93}

Endemic skeletal fluorosis has been reported predominantly in tropical countries with varying concentrations of fluoride in drinking water (1 to >10 mg/l); however, nutritional deficiencies, fluoride intake from other sources, and hard manual labor play an etiological role in the disease.^{14,87,94} Two cases of crippling fluorosis associated with excessive consumption of fluoridated water and tea have been reported in the U.S.^{95,96} Fluoride intakes by these individuals were reasonably estimated to have exceeded 15 to 20 mg/d for 20 years.⁸¹

Fluoride supplements have been used clinically for the treatment of osteoporosis.^{97,98} Chronic ingestion of 30 to 50 mg/d of fluoride for 2 to 3 years causes increased trabecular and cortical bone formation, but about 10 to 30% of patients also exhibit rheumatic pain and/or gastric upset. Osteomalacia has also been observed at these dose levels.^{97,99}

3. Hypersensitivity

Hypersensitivity reactions have been reported following exposure to fluoridated water, toothpastes, and fluoride supplements.^{71,72,100,101} Symptoms include skin rash, inflammation of oral mucosa, gastrointestinal irritation, and headache, which subsided after discontinued use of these products. Most reactions occurred following doses of about 0.5 to 1 mg fluoride in fluoride drops, tablets, or toothpaste.^{100,101} In a preliminary double-blind study, adverse reactions to ingestion of drinking water containing fluoride at 1 mg/l were reported to occur in "certain" of 60 individuals selected from a group of 300 test subjects with suspected sensitivity to fluoride.⁷¹ However, this study did not report the rate of false-positive or false-negative reactions among subjects, and test subjects believed that they were sensitive to fluoride, which could have biased the results. A review of these studies by the National Academy of Sciences⁹³ noted several methodological deficiencies, including the lack of control subjects, study selection bias, and uncontrolled exposure to other agents in fluoride dentrifices and/or supplements. The available data suggest that some individuals may react idiosyncratically to fluoride; however, the prevalence of these reactions among the population is unknown. Further studies on possible hypersensitivity reactions to fluoride and the prevalence of these reactions among the general population are required.

4. Renal Effects

Several studies have shown that persons with renal insufficiency have elevated plasma fluoride levels compared with normal individuals,¹⁰² and are at increased risk of developing systemic fluorosis.^{74,96} Dental fluorosis has been reported in individuals with nephrogenic diabetes insipidus who consume large volumes of water containing 0.5 to 1.0 mg fluoride per liter.^{103,104} Two cases of osteosclerosis and one case of crippling skeletal fluorosis have been reported in individuals with renal impairment and a history of excessive intake (up to 8 l/d) of water containing approximately 2 to 3 mg/l of fluoride.^{74,96} Lantz et al.⁷³ recently reported a case of renal failure and osteosclerosis associated with long-term daily consumption of 2 to 4 l of mineral water containing 8.5 mg/l of fluoride. These studies indicate that persons with renal impairment are at increased risk of developing fluorosis. However, a causal association between excessive fluoride exposure and induction or exacerbation of renal disease cannot be drawn from these data.

Several epidemiological studies have evaluated the effect of chronic exposure to fluoride on kidney disease and function.^{14,67} No evidence of an increased frequency of kidney disease or renal dysfunction has been observed in several studies on U.S. populations exposed to up to 8 mg/l fluoride in drinking water when compared with non-fluoridated areas (<0.3 mg/l).^{89,105,106} Renal impairment has been observed in areas of endemic skeletal fluorosis.¹⁰⁷ Acute renal dysfunction has been reported at high plasma fluoride levels (>0.6 mg/l) following exposure to certain volatile fluorinated anesthetic agents.¹⁰⁸

Functional and structural changes in the kidneys of experimental animals have been observed following chronic exposure to fluoride.¹⁰⁹⁻¹¹¹ Inflammatory changes in the renal glomeruli were reported in mice receiving fluoride at approximately 1 mg/kg/d in drinking water (4.5 mg/l) for 3 months.¹⁰⁹ No effects on renal structure were observed in rats exposed to fluoride at 2.5 mg/kg/d (50 mg/l) for 6 months; however, renal tubular necrosis was observed at the 5 mg/kg/d (100 mg/l) dose level.¹¹¹

5. Miscellaneous Studies

Several long-term epidemiological studies in the U.S. and England have compared general health and overall mortality rates in fluoridated (0.7 to 5.8 mg/l) and nonfluoridated (\leq 0.3 mg/l) communities.^{89,106,112,114} No effects on normal growth and development, general health, or cause-specific mortality rates were detected. An association between repetitive strain injury and fluoride intake has been proposed based on preliminary findings of higher fluoride levels in alveolar bone samples from affected individuals than in controls;⁷⁵ however, these data are insufficient to support a causal association. Three patients receiving sodium fluoride at 16 to 150 mg/d for periods of 1 to 36 months exhibited monocytoid giant cells in the bone marrow. Within 3 months of discontinuation of fluoride therapy, the bone marrow was normal.¹¹⁵

Additional adverse effects observed in experimental animals include decreased growth rate, anemia, and effects on collagen synthesis, and thyroid function.^{14,110,116-121} Decreased growth was reported in mice exposed to fluoride at 20 mg/kg/d (100 mg/l) in drinking water for 8 weeks¹²² and in rats receiving approximately 5 mg/kg/d (100 mg/l in water plus 3 mg/kg in diet) for 6 months.¹¹¹ Anemia was observed in rabbits given intragastric doses of 4.5 mg fluoride per kilogram per day for 1 year.¹²³ Abnormal osteoid formation and defective collagen biosynthesis have been reported in rabbits administered at least 4.5 mg fluoride per kilogram per day for up to 10 months.¹¹⁹⁻¹²¹ Structural and functional changes in the thyroid have been reported in several species at dose levels exceeding 5 mg/kg/d (>50 mg/l).^{110,117}

C. Carcinogenicity

1. Epidemiological Studies

There have been many epidemiological studies attempting

to correlate the cancer mortality in large population groups with the concentrations of fluoride in the water supply for those population groups (often called correlational or ecological studies). Several of these correlational studies have evaluated cancer mortality data from cities in the U.S. with differing concentrations of fluoride in their water supplies. In 1975, Yiamouyannis and Burk⁷⁸ initially reported that cancer mortality was higher in ten U.S. cities with fluoridated water supplies than in 10 cities without fluoridated water supplies. The National Cancer Institute (NCI) reanalyzed these cancer mortality data using different statistical methods and found no significant increases in cancer mortality in the cities with fluoridated water.¹²⁴ In addition, Hoover and co-workers evaluated cancer mortality in Texas, comparing counties with higher concentrations of naturally occurring fluoride in their water supplies (0.7 to 1.2 mg/l; 1.3 to 1.9 mg/l; >2.0 mg/l) with counties with lower concentrations (<0.7 mg/l) and found no evidence of increased cancer mortality in the counties with higher concentrations. The upper limit of fluoride concentration was not defined in this study.

Due to the controversy over these conflicting results, the cancer mortality data for U.S. cities have subsequently been reanalyzed by several other researchers utilizing slightly different techniques and/or modifications in the area or years being compared. These subsequent reports have supported the NCI conclusions in finding no significant increase in cancer mortality in the cities with higher concentrations of fluoride.¹²⁵⁻¹³² Correlational studies evaluating populations in other countries also support these findings. Australian researchers compared cancer mortality from 1970 to 1972 in 10 localities with fluoridated water supplies (fluoridation began around 1956) with mortality in 10 localities without fluoridated water (<0.7 mg/l) and found no evidence of an increase in cancer mortality in the fluoridated localities.¹³³ Canadian researchers evaluated cancer mortality in 100 Canadian cities from 1954 to 1973 in relation to the fluoridation of their water supplies and found no evidence of increased cancer mortality from fluoridation.¹³⁴ New Zealand researchers examined cancer mortality from 1961 to 1976 in people aged 45 years or over in six areas of New Zealand, where fluoridation was initiated in 1967 (population 45 or over, approximately 165,000) in comparison with four nonfluoridated areas (population 45 or over, approximately 80,000).¹³⁵ They found no evidence that cancer mortality rate was increasing in the fluoridated areas compared with the non-fluoridated areas.

Several correlational studies also have been conducted in Great Britain. In one study, cancer mortality for selected time periods in Birmingham (whose water supply was fluoridated since 1964) was compared with the cancer mortality in six other cities in England and Wales without fluoridated water supplies.¹³⁶ The increase in overall cancer mortality in Birmingham over the time period was similar to the average increase for the other six cities. Another study evaluated the

cancer mortality in Anglesey, where the water supply was fluoridated (0.9 mg/l) over the period 1955 to 1966, comparing cancer mortality in the period before fluoridation (1949 to 1953) with that in a period more than 20 years after fluoridation (1979 to 1983).¹³⁷ This study showed no evidence of increased mortality from respiratory cancer, cancer of the stomach, or cancer of all other sites in Anglesey when compared with cancer mortality in England and Wales for the same period. Another British study evaluated cancer mortality (all cancers combined plus 12 specific cancer sites) from 1969 to 1973 for 67 small areas in England, based on the concentrations of naturally occurring fluoride in their water supplies (categories: ≤ 0.2 vs. ≥ 1.0 mg/l; ≤ 0.1 vs. 0.5 to 0.99 mg/l) and found no evidence of increased cancer mortality with increasing concentrations of fluoride.¹³⁸

The incidence of cancer of the thyroid, kidney, stomach, esophagus, colon, rectum, bladder, bone, and breast in areas of England with a high natural fluoride level (1.0 mg/l and "over") in the water was compared with that in areas with low water fluoride levels (≤ 0.2 mg/l). No differences were detected. Similarly, no differences were found in cancer incidence between fluoridated and control districts in England and Wales, the U.S., Holland, and New Zealand.¹³⁹

Another potential source of information on the carcinogenicity of fluorides is the study of working populations exposed to fluoride. Some studies of workers in the aluminum industry (where workers may be heavily exposed to fluorides) have found an excess incidence of respiratory cancer, but the studies indicate that this excess is probably due to polynuclear aromatic compounds, not fluoride.¹⁴⁰

In summary, the epidemiological data on the relationship between fluoride exposure and cancer mortality include a large number of correlational studies evaluating cancer mortality in large population groups in relation to the concentration of fluoride in the water supply for these areas. The populations studied included groups exposed for over 20 years to artificially fluoridated water as well as groups who were exposed for well over 20 years to water supplies with high natural concentrations of fluoride (some of the latter had levels over 2.0 mg/l). This type of study has significant limitations, including the inability to account for migration into and out of the areas being studied and the inability to adequately assess other factors such as differences in industrialization or in personal risk factors, which may contribute to the incidence of cancer. In addition, some of these studies have focused on small populations and have not studied populations exposed to fluoride long enough to properly evaluate a carcinogenic effect. Despite these limitations, the overall evidence from these studies and from occupational studies provides no credible evidence that fluorides in drinking water increase cancer mortality.

Although the available epidemiological studies do not indicate any increased cancer risk from ingesting fluoridated water, further epidemiological study could be warranted to

address some of the weaknesses in the correlational studies (outlined above). Studies of individuals exposed to fluoridated water, which account for possible migration and for other cancer risk factors, would be useful in addressing concerns about this issue.

2. Animal Studies

There are only three studies that have attempted to evaluate the carcinogenicity of fluoride through oral administration to animals. The earliest study involved 50 female mice fed 900 mg/kg of sodium fluoride in their diet from 7 to 10 weeks of age until the mice were 97 to 100 weeks of age.¹⁴¹ An equal number of mice were fed a diet without fluoride and observed over the same period. Tumors of the mammary gland were found in 20 of the 40 treated animals and 37 of the 47 controls. A later study evaluated mice given varying amounts of fluoride in their drinking water for a period of 7 to 12 months.¹⁴² Of the mice exposed to fluoride, 59% died from mammary gland tumors compared with 54% of the controls. Of the mice receiving the highest amount of fluoride in their water, 63% (10 mg/l) died from mammary gland carcinomas compared with 50% of the controls. The most recent study evaluated 54 male and 54 weanling female mice given 10 mg sodium fluoride per liter in their drinking water for life against controls.¹⁴³ When the animals were sacrificed, tumors were found in 22 of 72 exposed mice compared with 24 of 71 controls.

All three of these studies have significant methodological limitations, including inadequate documentation of methods and results, incomplete selection of fluoride doses, and inadequate time period of observation. These deficiencies make it difficult to completely assess the possible carcinogenicity of inorganic fluoride in this type of study. A study on the lifetime exposure of rats and mice to fluoride has been completed by the National Toxicology Program and by others. Assessment for cancer has not been completed yet.

3. International Agency for Research on Cancer (IARC) Classification

In 1982, IARC reviewed the available evidence on the carcinogenicity of inorganic fluoride.¹⁰⁷ They concluded that the available data were "inadequate" for an evaluation of the carcinogenicity of sodium fluoride in experimental animals, and that studies of cancer incidence in populations with differing concentrations of fluoride in water "provide no evidence of an association between fluoride ingestion and mortality from cancer in humans".

D. Genotoxicity

The genotoxicity of fluoride has been reviewed.^{107,144-146} Fluoride lacked mutagenic activity in microbial systems (Ames test, *Saccharomyces cerevisiae* and rat hepatocytes,^{147,148} but produced mutations in mouse lymphoma cells at cytotoxic concentrations.¹⁴⁹ Chromosomal aberrations were not increased in

bone marrow or testicular cells of mice exposed to drinking water containing either 50 mg/l fluoride for five generations or 100 mg/l for 6 weeks.¹⁴⁷ However, increased aberrations (breaks and gaps) have been reported *in vitro*.^{150,151} Increased sister chromatid exchange activity was not observed in a variety of *in vivo* and *in vitro* cell systems,^{148,152-154} with one exception.¹⁵⁰ Negative results have also been reported in the mouse bone marrow micronucleus test.¹⁵⁵ Fluoride was noted both to increase^{150,151,156} and to have no effect^{148,157,158} on unscheduled DNA synthesis in cultured human and rodent cells. Fluoride lacked transformation activity in mouse embryo cells, but slightly increased transformation was reported in Syrian hamster embryo cells.¹⁵⁹ Poor cell growth and lack of positive control effects in the hamster cell assay decrease the value of these results. Nevertheless, Tsutsui et al.¹⁵⁰ have also reported transformation activity in Syrian hamster embryo cells. Most of the positive findings in the above assays were reported by a single research group (Tsutsui et al.), which predominantly observed effects at high concentrations, which also inhibited cell growth. Fluoride has been claimed to exert anticlastogenic¹⁶⁰ and antimutagenic¹⁶¹ activity on known genotoxic agents; however, the antimutagenic effects have been refuted as artificial.¹⁶² No data are available on the genotoxic effects of fluoride in exposed humans.

E. Effects on Cellular Enzyme Activities

Fluoride at millimolar concentrations affects the *in vitro*-determined activities of many cellular enzymes, including cholinesterase, glutamine synthetase, catalase, alkaline phosphatase, phosphorylase, acid phosphatase, pyrophosphatase, aconitase, esterases, creatine phosphokinase, muscle ATPase, glucuronidase, phosphomutase, enolase, succinate dehydrogenase, adenylyl cyclase, cytochrome *c*, lactate dehydrogenase, and carboxylase.¹¹⁰ Some enzymes such as pyrophosphatase,¹⁶³ acetylcholinesterase,¹⁶⁴ glucose-6-phosphate phosphohydrolase in the presence of aluminum ions,¹⁶⁵ and lactate dehydrogenase¹⁶⁶ are inhibited by fluoride, while others, such as adenylyl cyclase,¹⁶⁷ are activated.

The relevance of these findings to the effects of low chronic doses of fluoride is questionable, since it is unlikely that adequate cellular levels of fluoride to alter the enzyme activities would be attainable *in vivo*. However, administration of fluoride to animals has caused changes in enzyme activities. Sodium fluoride (35 mg/kg) increased rat hepatic and renal glucose-6-phosphatase activity two- to fourfold 3 h after administration, contrasting with reports of inactivation *in vitro*.¹⁶⁸ Glucose-6-phosphate dehydrogenase activity increased after 30 d of administration of 25 mg sodium fluoride per kilogram per day,¹⁶⁹ but monoamine oxidase and acetylcholinesterase activities were not altered. Much of the *in vivo* and even *in vitro* data on

fluoride effects on enzymes is contradictory, and the following results with adenylyl cyclase serve as an example.

In broken cell preparations of adipocytes, fluoride (10 mM) increased adenylyl cyclase activity by between 4- and 11-fold, but was ineffective when cells were whole.¹⁶⁷ In contrast, in whole cell preparations of hepatocytes, fluoride (0.15 to 10 mM) increased adenylyl cyclase activity by 1.6- to 5.9-fold.¹⁷⁰ *In vivo* acute administration of fluoride (0.05 and 0.10 mg/kg body weight) to humans produced maximal serum fluoride levels of 0.27 mg/l at 30 min after administration, without affecting adenylyl cyclase activity.¹⁷¹ Rabbits that received 10 mg sodium fluoride per kilogram per day for 6 months achieved serum fluoride levels of 0.38 mg/l and exhibited approximately twofold increases in liver and kidney and a threefold increase in bone adenylyl cyclase activity.¹⁷² Rats exposed to high concentrations of fluoridated drinking water (100 mg/l) for up to 8 weeks achieved blood fluoride levels of 0.12 mg/l, but exhibited no change in adenylyl cyclase activity as evidenced by urinary concentrations or the daily excretion of cyclic AMP.¹⁷³ Squirrel monkeys were administered distilled water containing fluoride at 0, 1, or 5 mg/l for 18 months.¹⁷⁴ The central nervous system, liver, and kidneys were examined histochemically. No histological effects of fluoride were detected. Enzymes involved with active transport, lysosomes, citric acid cycle, energy generation, anaerobic metabolism, and the pentose shunt were unaffected in the nervous system and liver. In the kidney, acid phosphatase activity was significantly increased at 5 mg/l, as were some activities of the citric acid cycle and the pentose shunt.¹⁷⁴

Overall, with one exception, the serum fluoride levels in animal studies required to produce effects on enzyme activities exceed the maximum levels of serum fluoride for humans drinking optimally fluoridated water by almost tenfold. There are no available data to indicate that, in humans drinking optimally fluoridated drinking water, the fluoride affects enzyme activities with toxic consequences.

A 1:1 complex of potassium fluoride and uracil, grown from 80% dimethyl sulfoxide — 20% water, has been used to demonstrate strong hydrogen bonding between the fluoride anion and the nucleotide base, thereby disrupting the self-association of uracil.¹⁷⁵ The potential for the fluoride anion to form strong hydrogen bonds with amides is supported by theoretical calculations and experimental spectroscopic data from studies where the potassium fluoride concentrations was 1 g/10 g solution.¹⁷⁸ These results formed the basis of suggestions that fluoride may disrupt hydrogen bonds in enzymes and DNA, thereby altering aspects of macromolecular structure with toxic consequence.¹⁷⁶ The finding of strong hydrogen bonding by fluoride under these extremely nonphysiological conditions was, however, not duplicated in a study conducted under normal

physiological conditions of pH and concentration.¹⁷⁷ There is no available evidence to support the hypothesis that strong fluoride hydrogen bonding properties, observed under extreme conditions, can lead to toxicity from exposure to chronic low levels of fluoride.

F. Reproductive/Developmental Toxicity

The epidemiological data relating fluoride exposure to effects on human reproduction, including fertility, and congenital malformations are largely inadequate due to limited sample sizes, inadequate exposure data, and other methodological problems; the available data have been reviewed.^{14,67,93,107,116} Early epidemiological studies by Rapaport^{76,77,178} reported a twofold higher incidence of Down's syndrome in communities using water supplies with naturally elevated fluoride levels (1 to 3 mg/l) over those with naturally low levels (0.1 mg/l). However, these reports have been criticized due to methodological errors such as poor case ascertainment, use of child's birthplace rather than maternal residence for defining exposure, and failure to classify Down's syndrome incidence by maternal age-specific groups.¹⁷⁹⁻¹⁸² Several more comprehensive and carefully conducted studies have not confirmed this association.^{179,183,187} These studies compared Down's syndrome incidence in communities having high fluoride concentrations (generally 0.7 to 2 mg/l) with those having low concentrations (generally \leq 0.3 mg/l) in their water supplies. In addition, a lack of association with other congenital malformations has been reported.^{179,185,186} No correlation was found between exposure to fluoridated water and general health and behavioral status in children evaluated from birth to 7 years of age.¹⁸⁸

Limited data are available on the reproductive effects of fluoride in animals. Decreased calving rates (30 to 50%) have been reported in young cows exposed to 0.55 mg fluoride per kilogram per day (5 mg/l) via drinking water for 4 years¹⁸⁹ or 1.56 mg fluoride per kilogram per day (77 mg/kg feed) via diet for 9 years, but not at 1.2 mg fluoride per kilogram per day (57 mg/kg feed).¹⁹⁰ Developmental effects, including stunted growth, abnormal bone morphology, and dental fluorosis, have been observed in the offspring of fluoride-intoxicated cows.¹⁹¹ Exposure to 20 mg fluoride per kilogram per day (100 mg/l) in drinking water impaired reproduction in mice,¹²² while neither 0.48 mg fluoride per kilogram per day (20 mg/l) via drinking water in sheep,¹⁹² nor 23 mg fluoride per kilogram per day (460 mg/kg feed) via diet in rats¹⁹³ was reported to produce adverse reproductive effects. Studies on guinea pigs exposed to 5 to 50 mg fluoride per liter in drinking water (1.7 to 17 mg/kg/d), indicate that uptake by the fetus is related to the length and magnitude of maternal exposure prior to gestation, with more fluoride transferred to fetal tissues during each successive pregnancy.¹⁹⁴

In summary, the lack of epidemiological and limited toxicological data on fluoride does not permit definitive conclu-

sions about the reproductive risks of fluoride exposure to humans. The available epidemiological studies do not support an association between consumption of fluoridated water and congenital malformations.

V. MECHANISMS OF FLUORIDE INTERACTION WITH TEETH

Elucidation of the mechanisms whereby fluoride interacts with and affects the viability of teeth should provide a basis for selection of its best route of administration. However, a number of mechanisms are apparently cooperative, incorporating both systemic and topical fluoride applications. These mechanisms involve the action of fluoride on hydroxyapatite of enamel, on dental plaque bacteria, on the enamel surface, and in altering tooth morphology.

A. The Action of Fluoride on Hydroxyapatite of Enamel

The solubility of enamel in acidic buffer is inversely proportional to the fluoride content of the teeth.⁷⁰ Fluoride stabilizes the crystal structure of the hydroxyapatite of enamel by providing additional and stronger hydrogen bonds.¹⁹⁵ Remineralization of teeth in the presence of fluoride more rapidly and effectively rehardens the enamel surface¹⁹⁶ and increases the average crystal diameter of the enamel. These effects of fluoride are probably a consequence of the partial substitution of fluoride for hydroxyl groups in the hydroxyapatite of the enamel to yield fluorapatite.⁷⁰ A combination of the occurrence of the highest level of fluoride substitution at the surface of the enamel and the coating of hydroxyapatite crystals with fluorapatite¹⁹⁷ could explain how relatively low fluoride concentrations could influence tooth decay. Systemic application of fluoride is required for substitution at the inner tooth surface during tooth development, while deposition at the surface of developed teeth is a consequence of topical application.^{70,198}

B. Action of Fluoride on Dental Plaque Bacteria

The enamel crystal surface undergoes continual erosion and reformation via ion exchanges.¹⁹⁹ Demineralization of enamel occurs when the pH at the plaque-enamel interface is low and remineralization predominates as the pH rises to neutrality.¹⁹⁸ Demineralization involves the transfer of calcium and phosphate ions from enamel into plaque. Bacterial glycolysis results in a fall in plaque pH, which is to a major extent prevented by fluoride.²⁰⁰ Thus, topical applications of fluoride facilitate remineralization by inhibiting bacterial glycolysis, thereby diminishing the potential for tooth decay.²⁰¹ The specific steps in glycolysis and the availability of sufficient concentrations of fluoride to inhibit those steps are still in question. Topically applied fluoride decreases levels of *Streptococcus mutans*, a virulent cariogenic bacterium.⁷⁰

C. The Action of Fluoride on Tooth Morphology and on the Enamel Surface

Claims that fluoride acts to prevent tooth decay by altering the morphology of teeth by lowering the free surface energy of teeth and by desorbing proteins or bacteria cannot be substantiated.⁷⁰

Current knowledge of the mechanisms of fluoride action suggest that both systemic and topical applications of fluoride affect tooth decay. The relative importance of the two routes of administration is not currently resolvable based on mechanistic considerations.

VI. CURRENT STANDARDS AND GUIDELINES

A variety of standards and guidelines for exposure to fluoride have been recommended to aid in the protection against dental caries and/or the development of adverse health effects. The National Research Council has estimated "adequate and safe" daily fluoride intakes to be 0.1 to 0.5 mg for infants less than 6 months of age, 0.2 to 1.0 mg for infants between 6 and 12 months, 0.5 to 1.0 mg for children between the ages of 1 and 3 years, 1.0 to 2.5 mg for 4- to 6-year-old children, 1.5 to 2.5 mg for children from 7 years to adulthood, and 1.5 to 4.0 mg for adults.¹⁶ The American Dental Association and the American Academy of Pediatrics have recommended a fluoride supplementation schedule for children that is designed to prevent dental caries without the development of objectionable dental fluorosis; these values are presented in Table 2.²⁰² The U.S. Environmental Protection Agency (EPA) established a maximum contaminant level (MCL) of 4 mg fluoride per liter for fluoride in drinking water, which was based on the avoidance of skeletal, but not dental, fluorosis.²⁰³ A secondary MCL, based on dental fluorosis (considered a cosmetic effect by EPA), was set at 2 mg/l.²⁰³ The World Health Organization recom-

Table 2
Supplemental Fluoride Dosage Schedule in Children According to Age and Drinking Water Fluoride Levels

Age (years)	Water fluoride concentration		
	<0.3 (mg/l)	0.3—0.7 (mg/l)	>0.7 (mg/l)
Birth to 2	0.25 ^a	0.0 ^a	0.0 ^a
2 to 3	0.50	0.25	0.0
3 to 13	1.00	0.50	0.0

^a Values are given in milligrams fluoride per day.

Adapted from the American Dental Association, *J. Am. Dent. Assoc.*, 113, 506, 1986.

mends a guidance value of 1.5 mg/l for fluoride in drinking water to avoid mottling of teeth.¹⁴ The MCL for community water supplies in New York State is 2.2 mg/l (set at twice the optimal level of 1.1 mg fluoride per liter).²⁰⁴ An occupational exposure limit of 2.5 mg fluoride per cubic meter, on a time weighted average basis has been established to protect workers from the adverse health effects associated with airborne fluoride compounds.²⁰⁵⁻²⁰⁷

VII. CRITERIA FOR EVALUATING EXPOSURE TO FLUORIDE

The predominant health concerns associated with chronic exposure to elevated levels of fluoride (≥ 2 mg/l in drinking water) are dental and skeletal fluorosis. There is no evidence that human exposure to fluoride in drinking water causes increased incidence of kidney disease or dysfunction (up to 8 mg/l), increased cancer mortality or incidence (reported to be >2 mg/l), genotoxic effects, alterations in cellular enzyme activities, and birth defects (up to 2 mg/l). The available epidemiological data on other adverse effects (i.e., hypersensitivity, reproductive performance, and increased susceptibility of individuals with renal insufficiency) are inadequate to evaluate risks associated with exposure to fluoride. Adverse effects in experimental animals (anemia, kidney necrosis, thyroid effects, decreased growth rate, impaired reproductive performance) generally occur at high dose levels (0.5 to 5 mg/kg/d).

Dental fluorosis is the most sensitive indicator of exposure to fluoride. Exposures to low levels of fluoride (1 to 2 mg/l) can contribute to moderate dental fluorosis in a small proportion of exposed children (approximately 1 to 2% at 1 mg/l and 10% at 2 mg/l). Severe dental fluorosis has only been consistently observed at levels exceeding 2.5 mg/l. The frequency and severity of dental fluorosis increases at higher concentrations. Fluoride at these concentrations (i.e., ≥ 1 mg/l) also contributes to reduced dental caries formation, which is a beneficial effect.

Several scientific groups have questioned whether moderate or severe dental fluorosis should be considered an adverse health effect. The U.S. EPA considered dental fluorosis to be a cosmetic effect rather than a health effect when deriving the MCL for fluoride in drinking water. However, the World Health Organization, the National Academy of Sciences, the American Dental Association, and the American Academy of Pediatrics have all recommended that exposures not exceed the optimal levels for dental caries benefits (see current standards and guidelines section) in order to avoid dental mottling, as well as adverse effects which may occur at higher levels.

At fluoride concentrations of 4 to 8 mg/l in drinking water, asymptomatic evidence of skeletal fluorosis (increased bone density) has been observed in a small proportion of the population (10 to 15% at 8 mg/l). The clinical significance of these

changes is questionable, since no observable adverse health effects have been associated with these changes. Although fluoride supplements have been used for the treatment of osteoporosis, there is no clear evidence that exposure to fluoride in drinking water has any beneficial effects on bone. Overt symptoms of skeletal fluorosis are generally not observed at dose levels below 20 mg/d (i.e., exposure to >10 mg/l for 20 years or more). However, those individuals with renal insufficiency who consume large quantities of fluoridated water are at an increased risk of developing skeletal fluorosis.

When evaluating the health risk associated with exposure to fluoride, it is important to also consider the benefits of fluoride on dental health. A fluoride concentration of 1 mg/l in drinking water is generally considered to be the optimal level for reducing dental caries without objectionable levels of dental fluorosis. In nonfluoridated communities, the use of fluoride supplements by young children has been recommended by the American Dental Association and the American Academy of Pediatrics to decrease the frequency of dental caries.

The margin of safety between typical fluoride intake by individuals living in fluoridated (1 mg/l) and nonfluoridated (<0.3 mg/l) areas and intakes associated with dental and skeletal fluorosis in humans is shown in Table 3. For this analysis, it was assumed that children and adults consume 1 and 2 l of water per day, respectively, and that exposure to fluoride from other sources is equivalent in fluoridated and nonfluoridated areas. Average exposures to fluoride from food and air are approximately 0.4 mg/d for adults and 0.2 mg/d for children. However, those individuals living near fluoride-emitting point sources who are exposed to much higher levels and those who consume greater volumes of water than assumed in this assessment are at increased risk of developing fluoride-induced health effects.

Children living in fluoridated areas (1 mg/l) or receiving fluoride supplements (0.5 to 1.0 mg/d) have a 1.5- to 3-fold margin of safety over levels associated with moderate (2 mg/l) or severe (>2.5 mg/l) dental fluorosis in a small proportion of the population. Children living in nonfluoridated areas who do not receive fluoride supplements have a higher margin of safety (seven- to eightfold) from dental fluorosis, but are at increased risk of developing dental caries. Since dental fluorosis is induced during the years of tooth formation, adults are not at risk to this effect unless they were exposed to elevated levels during childhood.

Adults living in fluoridated areas have a four- to eightfold margin of safety over levels shown to increase bone density in approximately 10 to 15% of the population (4 to 8 mg/l) and tenfold margin of safety over levels associated with clinical symptoms of skeletal fluorosis (20 mg/d). The margin of safety from preclinical and clinical stages of skeletal fluorosis among

Table 3
Margin of Safety between Exposure to Fluoride by Individuals Living in Fluoridated (1 mg/l) and Nonfluoridated (<0.3 mg/l) Areas and Fluoride Levels Causing Dental and Skeletal Fluorosis

Exposures	Margin of safety ^a		
	Dental fluorosis ^b		
Children ^c	Moderate	Severe	
	Fluoridated	2	2.5
	Nonfluoridated + 0.5 to 1.0 mg fluoride per day supplements	2.5—1.5	3.1—1.9
Nonfluoridated without supplements	6.7	8.3	
Adults ^c	Skeletal fluorosis ^d		
	Preclinical	Clinical	
	Fluoridated	4—8	10
Nonfluoridated	13—26	33	

^a Margin of safety = $\frac{\text{effect level}}{\text{estimated daily exposure}}$

^b 10% prevalence of moderate fluorosis at 2 mg/l; severe fluorosis observed at >2.5 mg/l. Effects are not applicable for adults since fluorosis is only induced during years of tooth formation.

^c Assumes children and adults consume 1 and 2 l of water per day, respectively, and exposure to fluoride from other sources is equivalent in fluoridated and nonfluoridated areas.

^d Preclinical changes in bone density at 4 to 8 mg/l (10 to 15% prevalence at 8 mg/l); clinical symptoms occur at intakes exceeding 20 mg/d for 20 years. Effects have not been reported in U.S. children exposed to up to 6 mg/l.

adults living in nonfluoridated areas is 13- to 26- and 33-fold, respectively. The clinical significance of asymptomatic increases in bone density is questionable; however, clinical stages of skeletal fluorosis clearly represent an adverse health effect.

VIII. SUMMARY

This summarizes current knowledge of the benefits and risks of fluoride ingestion.

The preponderance of evidence indicates that fluoride can reduce the incidence of dental caries and that fluoridation of drinking water can provide such protection. Due to the ubiquitous nature of exposures to fluoride sources other than drinking water, it is currently impossible to draw firm conclusions regarding the independent effect of fluoride in drinking water on caries prevalence using an ecologic study design.

Moderate dental fluorosis occurs in 1 to 2% of the population exposed to fluoride at 1 mg/l in drinking water and in about

10% of the population at 2 mg/l; moderate/severe fluorosis occurs in variable percentages ranging up to 33% of the population exposed to fluoride at 2.4 to 4.1 mg/l in drinking water. The issue of whether moderate or severe dental fluorosis represents an adverse health effect is still controversial.

There is no evidence of skeletal fluorosis among the general U.S. population exposed to drinking water fluoride concentrations lower than 4 mg/l. Radiographically detected osteosclerosis after chronic exposure to fluoride in drinking water at 8 mg/l was not associated with clinical symptoms. Reports of crippling skeletal fluorosis associated with low concentrations of fluoride in drinking water in tropical countries have been attributed to other dietary factors.

The available data suggest that some individuals may experience hypersensitivity to fluoride-containing agents. Further studies on hypersensitivity are required.

There is no evidence of increased incidence of renal disease or renal dysfunction in humans exposed to up to 8 mg fluoride per liter in drinking water. Structural changes in kidneys of experimental animals have been detected at doses exceeding 1 to 5 mg fluoride per kilogram per day.

Based on four case reports, individuals with renal insufficiency who consume large volumes of naturally fluoridated water at 2 to 8 mg/l are possibly at increased risk of developing skeletal fluorosis. Studies on the effects of fluoride in individuals with renal insufficiency are needed.

There is no evidence that chronic exposure to concentrations of fluoride reported to be >2 mg/l in drinking water increases human cancer mortality or incidence. A study of lifetime exposure to fluoride on cancer incidence in rats and mice has been completed, but assessment for cancer has not been completed.

There is no evidence that fluoride is genotoxic except in some *in vitro* assays at cytotoxic concentrations.

There is no *in vivo* evidence that fluoride affects human cellular enzyme activities. Fluoridated drinking water at 5 mg/l slightly increased renal enzyme activities in monkeys when ingested chronically for 18 months. There is no evidence that fluoride hydrogen bonds to cellular macromolecules under physiological conditions with toxic consequences.

There is no evidence that exposure of pregnant mothers to fluoride at up to 2 mg/l in drinking water causes Down's syndrome or other congenital malformations in offspring. Studies at higher concentrations have not been undertaken. There are no studies relating human reproductive performance to fluoride exposure.

Children living in fluoridated areas or receiving fluoride supplements (0.5 to 1.0 mg fluoride per day) have a 1.5- to 3-fold margin of safety from moderate or severe dental fluorosis. A higher margin of safety (seven- to eightfold) exists for children living in nonfluoridated areas who do not receive fluoride supplements.

The margin of safety over preclinical and clinical stages of

skeletal fluorosis among adults living in fluoridated areas is 4- to 8-fold and 10-fold, respectively; adults living in nonfluoridated areas have a 13- to 26-fold and 33-fold margin of safety from these effects, respectively.

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