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Fluoride

Guideline

The maximum acceptable concentration (MAC) for fluoride in drinking water is 1.5 mg/L.

Identity, Use and Sources in the Environment

In the free state, fluorine is a pale yellow diatomic gas. Fluorine is never found in this form in nature, because it is very chemically reactive and combines with every other element except the inert gases. It is the 13th most abundant element, commonly occurring in the minerals fluorspar (CaF_2), cryolite (Na_3AlF_6) and fluorapatite ($3Ca_3(PO_4)_2 \cdot Ca(F,Cl)_2$).[1,2]

Fluorine is used in aluminum, steel, glass, enamel, brick, tile, pottery and cement manufacturing; fluorinated chemical and phosphate fertilizer production; and metal casting, welding and brazing.[3,4] Sodium fluoride (NaF) is used in various pesticide formulations, including insecticides and wood preservatives.[5] Fluoride-containing compounds are employed in the artificial fluoridation of drinking water for the prevention of dental caries.[6] Fluoride-containing dental products are now widely available, including toothpaste, supplements, mouth rinses and professionally applied gels and varnishes.[7] Fluoride (primarily as NaF) has also been used in the treatment of osteoporosis.[8]

Both natural and anthropogenic sources can contribute fluoride to soil, air, water and food. About 23 500 t of inorganic fluorides are released from anthropogenic sources in Canada each year,[4] whereas global volcanic sources are estimated to release 60–6000 kt annually.[9] Fluoride can occur naturally in surface waters as a result of the deposition of particulates from the atmosphere and the weathering of fluoride-containing rocks and soils. Groundwater can also contain high concentrations of fluoride owing to leaching from rocks. Chemical manufacturing plants and waste ponds can contribute fluoride to raw water sources directly through effluents or indirectly through volatilization.[3,10] Free fluoride ions predominate in aqueous solutions, but both ionic (i.e., inorganic) and nonionic forms of fluoride can be present in plant and animal tissues.[8,11]

Exposure*

Surveys conducted in 1984–1989 in several provinces found mean concentrations of fluoride** in non-fluoridated drinking water ranging from <50 µg/L (detection limit) in British Columbia (not detected in three locations) and Prince Edward Island (detected in four of 13 locations; <50–70 µg/L) to 210 g/L in the Yukon (<30–650 µg/L; detection limit <30 µg/L).[12–14] Elevated levels of naturally occurring fluoride in drinking water are relatively infrequent in Canada, although communities in Quebec, Saskatchewan and Alberta have recorded concentrations as high as 2520–4350 µg/L.[15] In 1986, artificially fluoridated drinking water was supplied to approximately 38% of the Canadian population.[15] Between 1986 and 1989, average fluoride concentrations in fluoridated drinking water across Canada ranged from 730 µg/L (600–800 µg/L) in Newfoundland and Labrador (three locations) to 1250 µg/L (1200–1300 µg/L) in the Yukon (two locations).[15–18]

Typical fluoride concentrations in fresh and cooked foods from Canada and the United States include 0.01–0.80 µg/g for dairy products; 0.01–0.58 µg/g for fruit; 0.04–4.57 µg/g for meats, fish and eggs; 0.05–0.13 µg/g for fats; and 0.02–0.86 µg/g for sugar-based foods.[19,20] A mean fluoride concentration of 0.54 µg/g (543 µg/L; range <0.05–5.85 µg/g) was recorded in a 1990 survey of 172 bottled waters obtained across Canada.[21]

The fluoride concentration of water used to reconstitute or prepare beverages and dry concentrates can greatly influence their fluoride content.[22–24] In the United States, fluoride concentrations in infant formulas were found to range from 0.127 mg/L for ready-to-use milk-based formulas to 0.854 mg/L for soy-based powdered formula prepared using water containing fluoride at a concentration of 1.0 mg/L.[25] A Canadian survey found that women consuming non-fluoridated drinking water (<0.16 ppm [mg/L] fluoride) produced milk with a

* Most of the exposure information presented in this section has been derived from studies previously reviewed and critiqued in reference 39.

** Unless otherwise specified, concentrations of fluoride refer to inorganic fluoride.

mean fluoride concentration of 4.4 ng/g (µg/L), whereas breast milk from women consuming fluoridated drinking water (1 mg/L fluoride) contained fluoride at a concentration of 9.8 ng/g.[26]

No Canadian data are available on fluoride concentrations in indoor air. Average monthly concentrations of fluoride (gaseous and particulate) in ambient air reported for a residential area of Toronto (Ontario) in 1981 ranged from 0.01 to 0.05 µg/m^3, with a mean of 0.03 µg/m^3.[27]

Canadian estimates of mean fluoride concentrations in soil range from 6 ppm (µg/g) for a forest in Newfoundland (depth and range not specified) to 309 ppm (63–1000 ppm at depths of 0–130 cm) for 23 Canadian Soil Survey Committee (CSSC) reference samples.[28,29]

The most commonly used fluoride-containing dental product is toothpaste. At least 95% of the toothpastes sold in North America contain fluoride as NaF and/or disodium monofluorophosphate (MFP, or Na_2PO_4F), with an effective fluoride concentration of approximately 1000 ppm (µg/g).[30–34] The mean amount of toothpaste ingested per brushing by children 1–4 years of age ranges from 0.13 to 0.39 g. In contrast, adults 20–35 years of age ingest an average of 0.04 g toothpaste per brushing.[35]

Other fluoride-containing dental products include fluoride supplements (NaF tablets or drops) for children residing in non-fluoridated communities,[36,37] fluoride mouth rinses, which are generally used in school-based programs in areas with high caries rates,[38] and topical fluoride gels, which are usually applied once or twice a year by dentists.[33]

Table 1.
Estimated daily intake of fluoride for the 7 month to 4 year and 20+ year age groups in the general population of Canada[a]

		Daily intake of fluoride from various sources (µg/kg bw per day)						Proportion of total daily intake allocated to drinking water[g]
Age group	Type of community	Drinking water[b]	Air[c]	Soil[d]	Food[e]	Toothpaste[f]	Total	
7 months – 4 years[h]	Non-fluoridated	3.08–12.92	0.01	0.02–1.19	22.30	20.00 –60.00	45.41–96.42	0.04–0.23 (0.15)[i]
	Fluoridated	44.92–76.92	0.01	0.02–1.19	22.30	20.00–60.00	87.25–160.42	0.35–0.65 (0.50)[i]
20+ years[h]	Non-fluoridated	1.07–4.50	0.01	0.002–0.09	30.08	1.14	32.30–35.82	0.03–0.13 (0.08)[i]
	Fluoridated	15.64–26.79	0.01	0.002–0.09	30.08	1.14	46.87–58.11	0.33–0.46 (0.40)[i]

[a] Daily intakes derived from data presented in Table 11 of reference 39.

[b] Estimated using mean fluoride concentration ranges for non-fluoridated (i.e., <50 µg/L for British Columbia and Prince Edward Island to 210 µg/L in the Yukon)[12–14] and fluoridated (i.e., 730 µg/L in Newfoundland and Labrador to 1250 µg/L in the Yukon)[15–18] communities in Canada, assuming that individuals from the 7 month to 4 year and 20+ year age groups consume 0.8 and 1.5 L of drinking water per day, respectively.[40]

[c] Combined intake from both indoor and ambient air. Indoor air concentrations assumed to be equivalent to ambient air concentrations.[39] Estimated intakes calculated from the mean ambient air concentration in Toronto (0.03 µg/m^3),[27] assuming that individuals from the 7 month to 4 year and 20+ year age groups breathe 5 and 20 m^3 of air per day, respectively.[40]

[d] Estimated from the range of mean fluoride concentrations in soil recorded for a forest soil in Newfoundland and 23 Canadian Soil Survey Committee (CSSC) reference soil samples (6–309 µg/g),[28,29] assuming that individuals from the 7 month to 4 year and 20+ year age groups consume 50 and 20 mg of soil per day, respectively.[40]

[e] Estimated using survey data on the concentrations of fluoride in various food groups in Canada and the United States[19,20] and estimates of the daily consumption of those food groups by the 7 month to 4 year and 20+ year age groups.[40]

[f] Calculated from the estimates of mean amounts of toothpaste ingested per brushing (i.e., 0.13–0.39 g and 0.04 g for the 7 month to 4 year and 20+ year age groups, respectively),[35] an effective fluoride concentration of 1000 µg/g for fluoridated toothpastes sold in Canada[34,41] and the assumption that both age groups brush their teeth an average of twice a day.[39]

[g] Calculated as follows:

Minimum allocation to drinking water = lowest daily intake from drinking water ÷ (lowest daily intake from drinking water + daily intake from air + highest daily intake from soil + daily intake from food + highest daily intake from toothpaste)

Maximum allocation to drinking water = highest daily intake from drinking water ÷ (highest daily intake from drinking water + daily intake from air + lowest daily intake from soil + daily intake from food + lowest daily intake from toothpaste)

[h] Assumed body weights: 7 month to 4 year age group, 13 kg bw; 20+ year age group, 70 kg bw.[40]

[i] Average.

The estimated daily intake of fluoride from drinking water, air, soil, food and toothpaste for two age groups — 7 months to 4 years and 20+ years — in the general Canadian population is shown in Table 1. Daily fluoride intakes from supplements, mouth rinses and gels were not estimated, as the available data on the proportion of the general population using these products or the amount of fluoride ingested from them were considered inadequate. However, regular supplement use in accordance with either Canadian Paediatric Society or Canadian Dental Association recommendations could add as much as 19–76 µg/kg bw per day to the daily fluoride intakes of preschool children in non-fluoridated communities.[36,37] For children less than 6 months of age with a body weight of 7 kg and a daily consumption of 0.75 L of formula or breast milk, daily fluoride intake can be estimated to range from 13.6 to 91.5 µg/kg bw for formula and from 0.47 to 1.05 µg/kg bw per day for breast milk.[39]

Analytical Methods and Treatment Technology

Several methods are available for measuring fluoride in drinking water, including ion-selective electrode, SPADNS colorimetric, complexone and ion chromatographic methods. The ion-selective electrode (suitable for 0.1–>10 mg/L)[42] and SPADNS colorimetric (suitable for 0.05–1.4 mg/L)[42] methods are most often employed for routine monitoring. The analytical range of the complexone method is 0.1–2.0 mg/L. Ion chromatography is not usually recommended for routine fluoride measurements because of difficulties with quantitation at low concentrations and interferences from simple organic acids, but it may be satisfactory if special techniques are employed, such as dilute eluent or gradient elution.[42]

Methods to remove fluoride from drinking water include adding chemicals during coagulation or softening to remove fluoride in the flocs, ion exchange or adsorption processes and demineralization techniques, such as reverse osmosis and electrodialysis.[43] Adsorption with activated alumina is probably the most effective and frequently used technique in municipal treatment systems.[43–45] Effluents of <1 mg/L have been obtained from raw water containing 5–8 mg/L at full-scale facilities using this technique; in practice, the upper limit for influent fluoride concentration is 10 mg/L.[43] Bone char is also used for adsorption, but the medium is more expensive, has a lower adsorption capacity and is less stable in continuous use than activated alumina.[43,45]

In Canada, artificial fluoridation is generally carried out by supplementing raw water with NaF, hydrofluosilicic acid (H_2SiF_6) or sodium silicofluoride (Na_2SiF_6).[44,46]

Health Effects*

Essentiality

Although Health Canada has classified fluoride as an essential element in the past,[47] it now recommends that fluoride requirements should "only be based on the beneficial effect on dental caries" and notes that "attempts to demonstrate its essentiality for growth and reproduction in experimental animals have not been successful."[48] Similarly, the U.S. National Research Council considers fluoride to be a "beneficial element for humans."[49]

Absorption, Distribution and Excretion

Ingested NaF is rapidly absorbed from the gastrointestinal tract.[50–53] The extent of dietary fluoride absorption was greater than 90% in balance studies with human volunteers.[54,55] In both adults and children, peak plasma levels were reached 30–60 minutes after the ingestion of doses ranging from 0.5 to 10 mg fluoride (as NaF).[56–58] The water solubility of fluoride compounds can influence their absorption; NaF is more readily absorbed than the less soluble CaF_2 and MFP.[11,59]

The plasma half-life of fluoride in humans and rabbits ranges from 2 to 11 hours following single or multiple oral doses of NaF (3.0–40 mg fluoride).[57,60] Up to 75% of absorbed fluoride may be deposited in calcified tissues, with the highest deposition found in children with active bone growth or individuals consuming non-fluoridated drinking water.[61] Approximately 99% of total body fluoride is localized in calcified tissues (i.e., bones and teeth), where it is substituted for hydroxyl ions (OH^-) in hydroxyapatite, forming fluorapatite.[62–65] The dose, duration of exposure and turnover rate of skeletal components all affect calcified tissue fluoride concentrations.[54,66] Although bone fluoride concentrations increase with age, the amount retained on a daily basis is inversely related to age; this is due to the greater surface area for fluoride uptake in hydrated young bone and the increased rate of resorption over formation in the elderly.[67] Fluoride can be mobilized from bone through a relatively rapid interstitial ion-exchange mechanism or a much slower bone remodelling process.[68]

Many of the factors affecting the uptake and retention of fluoride in bone also affect fluoride concentrations in teeth, with the exception that tooth enamel and dentin do not undergo continuous remodelling.[11] Enamel fluoride concentrations decrease with distance from the tooth surface and also vary with location, surface wear, age and degree of exposure to systemic and topical fluorides.[69,70]

* Most of the health effects information presented in this section has been derived from studies previously reviewed and critiqued in reference 39. Emphasis has been given to studies (laboratory animal and human) dealing with oral exposures to fluoride.

Mean iliac bone fluoride concentrations recorded for adults (60 years of age) consuming non-fluoridated (<0.1 ppm) and fluoridated (0.97 ppm) drinking water were 351 mg/kg (106–790 mg/kg) and 1090 mg/kg (347–2360 mg/kg), respectively.[71] Surface enamel fluoride concentrations were reported to be 740–1400 mg/kg and 1351–2100 mg/kg for adults 20 years of age or older from communities with drinking water fluoride concentrations of 0.1 and 1 ppm, respectively.[72] The concentration of fluoride in dentin is generally 2–3 times higher than that in enamel.[73]

Fluoride is excreted primarily via the urine, with perspiration, saliva, breast milk and faeces making smaller contributions to daily body clearance.[67,74–76] In adult humans, approximately 50–75% of an oral dose of fluoride appears in the urine within 24 hours after ingestion.[57,77,78] Under conditions of relatively constant exposure, urinary excretion correlates well with drinking water fluoride levels and is often used as an indicator of exposure.[11]

Fluoride is readily transferred from mother to foetus across the placenta.[11]

Acute and Chronic Toxicity

In humans, acute ingestion of fluoride can result in nausea, vomiting, abdominal pain, diarrhoea, fatigue, drowsiness, coma, convulsions, cardiac arrest and death.[10,11,63,67,79] Effects are most severe following ingestion of the more soluble fluoride salts.[11] The LD_{100} for fluoride in the average adult has been estimated to be 32–64 mg/kg bw (as NaF), and deaths in children have been reported after ingestion of as little as <5–30 mg/kg bw.[11,67] Oral fluoride LD_{50}s in rats and mice range from 25.5 to 45.7 mg/kg bw for stannous fluoride (SnF_2),[80–82] from 31 to 101 mg/kg bw for NaF[82–86] and from 54 to 102 mg/kg bw for MFP.[82,84,86,87]

In a comprehensive National Toxicology Program (NTP) chronic toxicity/carcinogenicity bioassay, groups of male and female F344/N rats and $B6C3F_1$ mice (70–100 per sex per dose) were exposed to drinking water containing 0, 25, 100 or 175 ppm NaF for 2 years (estimated intakes 0.2, 0.8, 2.5 and 4.1 mg/kg bw per day for male rats, 0.2, 0.8, 2.7 and 4.7 mg/kg bw per day for female rats; 0.6, 1.7, 4.9 and 8.1 mg/kg bw per day for male mice, 0.6, 1.9, 5.7 and 9.1 mg/kg bw per day for female mice). Bone ash fluoride content increased in both species during the course of the study, with terminal concentrations ranging from 0.44 (controls) to 5.26 (high-dose group) µg/mg in male rats, from 0.55 to 5.55 µg/mg in female rats, from 0.72 to 5.69 µg/mg in male mice and from 0.92 to 6.24 µg/mg in female mice. The high-dose female rats had a significantly higher incidence of osteosclerosis and a slight but significant increase in brain to body weight ratio compared with controls. Serum alkaline phosphatase activity was increased in high-dose male mice after 66 weeks and in high-dose female mice after 27 and 66 weeks.[88] Estimated no-observed-adverse-effect levels (NOAELs) were 2.7 and 4.1 mg/kg bw per day for the female and male rats, respectively, and 5.7 and 4.9 mg/kg bw per day for the female and male mice, respectively.[39]

In another chronic toxicity/carcinogenicity bioassay, NaF was administered via the diet to groups of male and female Sprague-Dawley albino rats (70 per sex per dose) and CD-1 mice (60 per sex per dose) for 95 weeks (male rats and mice), 99 weeks (female rats) or 97 weeks (female mice). Estimated fluoride intakes for both rats and mice were 0.1 (low-fluoride diet control), 1.8, 4.5 and 11.3 mg/kg bw per day. At the end of the study, bone ash fluoride content ranged from 0.5 (controls) to 16.7 (high-dose group) µg/mg in male rats, from 0.5 to 14.4 µg/mg in female rats, from 1.5 to 13.2 µg/mg in male mice and from 1.0 to 10.6 µg/mg in female mice. Increased subperiosteal hyperostosis in the medium- and high-dose rats was the most notable non-neoplastic skeletal effect observed in the study. Other effects included reduced weight gain in the high-dose rats and hyperkeratosis and acanthosis in the stomachs of medium- and high-dose rats.[89,90] For the rats, a NOAEL was estimated at 1.8 mg/kg bw per day.[39]

Most of the available studies of potential non-neoplastic human health effects from chronic fluoride ingestion have focused on adverse effects on the skeleton, principally skeletal fluorosis and fractures. The data consist primarily of epidemiological studies of populations exposed to various concentrations of fluoride in drinking water, case reports of individuals exposed to drinking water containing elevated concentrations of fluoride and clinical studies of osteoporosis patients treated with NaF.

Skeletal fluorosis is an excessive accumulation of fluoride in bone associated with increased bone density and outgrowths (exostoses).[10] Fluoride incorporated into bone (i.e., as fluorapatite) produces a crystal lattice that undergoes less resorption (i.e., less soluble; more stable) and has an increased compression strength, but is more brittle and has a decreased tensile strength.[8,65] Characteristic signs and symptoms of skeletal fluorosis range from asymptomatic radiographic enlargement of spinal trabeculae in the preclinical form (stage I) to the severe calcification of ligaments, spine and joint deformities, muscle wasting and neurological defects observed in crippling skeletal fluorosis (stage III).[8] The more severe symptoms tend to be associated with the vertebral column in the lower, weight-bearing parts of the body.[91] Ashed bone fluoride concentrations may range from 3500 to 5500 mg/kg in stage I skeletal fluorosis to >8400 mg/kg in stage III.[8] Age, nutritional deficiencies, renal insufficiency, bone remodelling and the dose and duration of fluoride exposure can all influence the occurrence of the disease.[8,10,11,63,64]

Studies from the United States showed no evidence of skeletal fluorosis following the consumption of drinking water containing fluoride concentrations of 1.2 and 3.3–6.2 mg/L for 10 years and a lifetime, respectively.[92–95] In an older study conducted in Texas, radiographic evidence of osteosclerosis but no clinical signs of skeletal fluorosis were reported for 18% (n = 89) of people from a small town (Bartlett) who consumed drinking water containing 8 mg/L fluoride for an average of 37 years, whereas the incidence was only 4% (n = 101) for the population of a control town (Cameron) where the drinking water contained 0.4 mg/L fluoride.[96] X-rays of residents of Texas and Oklahoma who had consumed drinking water containing 4–8 mg/L fluoride indicated 23 cases of osteosclerosis "due to fluoride" but no cases of skeletal fluorosis.[97] In a recent review of available radiographic studies, Kaminsky *et al.*[63] concluded that for individuals in the United States who consumed drinking water containing ≤4.0 mg/L fluoride, there was no evidence of the skeletal changes associated with skeletal fluorosis.

Endemic crippling skeletal fluorosis has been reported in adults and children from areas of India, Africa and China where the fluoride concentrations in drinking water ranged from 3 to >20 mg/L.[8,11,63,98,99] As not all residents of these areas show signs of the disease, other factors, such as dietary deficiencies (e.g., protein, calcium, etc.) and other sources of daily fluoride intake, may be contributing to the development of the disease.[11,99,100]

A recent North American case report of stage I skeletal fluorosis involved a 54-year-old woman from Oklahoma who consumed drinking water containing 7–8 mg/L fluoride for 7 years.[101] Crippling skeletal fluorosis has been described in only five North American case reports over the past 40 years, all from the southwestern United States: three were associated with long-term consumption (40–>60 years) of drinking water containing elevated concentrations of fluoride (2.4–7.8 mg/L),[102–104] one involved a history of geophagia (eating soil)[105] and one gave no details on fluid or food consumption.[106] Although a recent review estimated the total fluoride intake for some of these patients to be 15–20 mg/d for 20 years[8] (estimated fluoride intake: 215–285 µg/kg bw per day[39]), only one case report, that of a 40-year-old woman with a history of geophagia, gave an estimate of daily fluoride intake (1.4 mg/d from drinking water, 4.2 mg/d from tea and 10.0 mg/d from soil consumption).[105] Several of the cases were complicated by pre-existing or associated renal disease, polydipsia and the daily consumption of large quantities of tea.[102–105]

Radiographic signs of stage I skeletal fluorosis were observed for 8/25 post-menopausal women treated for osteoporosis with a combination of 40–60 mg/d NaF (estimated fluoride intake: 260–389 µg/kg bw per day[39]), calcium and vitamin D_2 for a period of 18 months. Patients treated only with calcium and vitamin D_2 showed no evidence of skeletal fluorosis.[107] Kleerekoper and Balena[108] reported that, depending on whether there is concurrent supplementation with calcium and vitamin D_2, mild, asymptomatic osteomalacia may occur in osteoporotic patients administered NaF doses above 40 mg/d (estimated fluoride intake: 260 µg/kg bw per day[39]).

Possible associations between the occurrence of skeletal fractures (predominantly hip fractures in elderly persons) and the exposure of populations to fluoridated drinking water have been examined in a number of epidemiological studies of the ecological or geographical correlation type. Studies of this type can suffer from a number of weaknesses, such as a lack of information on individual fluoride intake (i.e., intake from other sources, such as food, dental products, etc.) within the fluoridated and control communities; geographical differences in various factors (e.g., smoking, lifestyles, environmental and occupational exposures, genetics, etc.) that could affect the occurrence of fractures; uncontrolled migration between fluoridated and control areas; and geographical variations in the quality of disease diagnosis and reporting.[8,39,109]

In a U.S. study, 216 counties with drinking water containing 0.7–1.2, 1.3–2.0, 2.1–3.9 or >4.0 mg/L fluoride (fluoridated) were compared with 95 counties where the drinking water contained <0.4 mg/L fluoride (non-fluoridated) for hip fracture hospitalization rates (1985–1986) in men and women over 65 years of age. The ratios comparing hip fracture rates in the fluoridated versus non-fluoridated counties increased from 1.016 for the 0.7–1.2 mg/L counties to 1.224 for the >4.0 mg/L counties, but they were significant ($p < 0.01$) only for counties with fluoride concentrations at or above 1.3–2.0 mg/L.[110] May and Wilson[111] found that the hip fracture rate in men and women older than 65 years from each of 438 U.S. counties with populations greater than 100 000 was positively correlated with the fraction of the population receiving fluoridated drinking water (up to 1.0 mg/L fluoride). However, a further analysis of 51 counties showed no relationship between hip fracture rate and duration of exposure, as the fracture rate was highest in counties with up to 10 years of exposure to fluoridated water, 20% lower for counties with 11–18 years of exposure and intermediate for counties with more than 18 years of exposure.[111]

Jacobsen *et al.*,[112] employing a time trend analysis approach, reported a slightly but significantly higher relative risk (RR) of hip fracture for white men (RR = 1.08, 95% confidence interval [CI] = 1.06–1.1) and white women (RR = 1.17, 95% CI = 1.13–1.22) older than 65 who resided in fluoridated counties (n = 129) in which the percentage of the population receiving fluoridated (1.0 mg/L) drinking water increased from <10% to >66% over 3 years compared with counties (n = 194) where >90% of the population was served with non-fluoridated (<0.3 mg/L) drinking water. Counties

starting fluoridation less than 5 years before the study had the highest fracture rates, whereas the rates declined for communities with progressively longer exposure periods.[112] A second study compared hip fracture rates in Rochester, Minnesota, 10 years prior to the initiation of drinking water fluoridation in 1960 and 10 years after. A total of 651 incident hip fractures were recorded in the 20-year period, 268 in men and 383 in women. Fluoridation was not associated with a risk of hip fracture in men and women 50 years of age or older (RR = 0.6, 95% CI = 0.42–0.85 in women; RR = 0.78, 95% CI = 0.73–1.66 in men).[113]

A comparison of hospital discharge rates between 1984 and 1990 for hip fracture in 65-year-olds between a fluoridated (1.0 mg/L) community and two non-fluoridated (<0.3 mg/L) communities in Utah gave age-adjusted risk ratios of 1.41 (95% CI = 1.00–1.81) for men (fluoridated: n = 19; non-fluoridated: n = 32) and 1.27 (95% CI = 1.08–1.46) for women (fluoridated: n = 65; non-fluoridated: n = 130) in the fluoridated versus non-fluoridated communities.[114] Suarez-Almazor *et al.*[115] conducted a study of hip fracture hospitalization rates in Alberta between 1981 and 1987 in men and women (≥45 years of age) from Edmonton, where fluoridation (to 1 mg/L) was initiated in 1967, and Calgary, where the drinking water contained 0.3 mg/L fluoride. Men from Edmonton in the age groups ≥45 or ≥65 years of age had significantly higher hip fracture rates (i.e., 12 and 13%, respectively; n = 827) than the corresponding age groups from Calgary (n = 700). However, there were no significant differences between the two cities when all age groups of women were considered or when both sexes were combined.[115]

A more powerful analytical approach was used to study the incidence of skeletal fractures in women from Iowa who lived for at least 5 years in either a fluoridated (i.e., 1 mg/L fluoride) or a naturally elevated fluoride (i.e., 4 mg/L fluoride) community.[93,116] Individual interviews and examinations were conducted in 1983–1984 to obtain detailed information on such factors as fracture history, water consumption, oestrogen use and bone mass and density. The estimated mean intake of fluoride from water-based beverages in the elevated-fluoride community was 72 µg/kg bw per day. For post-menopausal women (age 55–80 years), the incidence of skeletal fractures over the previous 10 years was significantly greater (p = 0.0001) in the elevated-fluoride (57/200) versus the fluoridated community (20/151). However, there was no significant difference between the two communities for fracture incidence in the 20–35 year age group (pre-menopausal).[93] Based on follow-up interviews and examinations 5 years later (1988–1989), the relative risk (age and body size adjusted) for any fracture in the post-menopausal group from the elevated-fluoride community (31/163) compared with the fluoridated community (11/121) was 2.11 (95% CI = 1.0–4.4). Hip fracture incidence for the post-menopausal group in the elevated-fluoride community was 5/163 compared with 0/121 for the fluoridated community. The 5-year (1983–1984 to 1988–1989) relative risk of fractures specifically in the hip, wrist or spine in the elevated-fluoride versus the fluoridated community was 2.7 (95% CI = 0.16–8.28) for the pre-menopausal and 2.2 (95% CI = 1.07–4.69) for the post-menopausal groups. The pre-menopausal women from the elevated-fluoride community experienced a greater loss of radial bone mass during the 5-year period than women in the same age group from the fluoridated community (i.e., 3.6% vs. 2.1%; p = 0.08).[116] Cauley *et al.*[117] reported no association between exposure duration and bone mineral density (with or without adjustment for age and body mass) or fracture history in a study in which they obtained details on the source of drinking water, bone mineral density and hip and wrist fracture histories for 1878 white women, ages 65–93, from the Pittsburgh, Pennsylvania, area. Less than half the women were exposed to fluoridated water (1.0 mg/L); for those exposed, the mean duration was 6 years (range 0–38 years).[117]

The incidence of skeletal fractures has been examined in several clinical case studies of osteoporosis patients undergoing treatment with NaF for extended periods of time. Inkovaara[118] found a 7.5% incidence of hip fracture in male and female geriatric patients (n = 146) administered NaF at 25 mg/d (estimated fluoride intake: 162 µg/kg bw per day[39]) for 5 months or 25 mg NaF twice weekly for 3 months, compared with a 3.0% incidence in controls (n = 169; p < 0.1). Inkovaara[118] also commented on an additional study that reported an incidence of hip fracture of 5/16 in osteoporosis patients (mean age 70) receiving 40–80 mg/d NaF (estimated fluoride intake: 260–520 µg/kg bw per day[39]) supplemented with calcium and vitamin D for 4 years compared with an incidence of 0/8 for controls. Post-menopausal women (mean age 67 years) treated with 40–60 mg/d NaF (estimated fluoride intake: 260–389 µg/kg bw per day[39]) supplemented with calcium and vitamin D for 18 months were observed to have an increased incidence of hip fracture compared with patients receiving only calcium and vitamin D (6/25 vs. 1/24; p > 0.05).[107] Mamelle *et al.*[119] found no significant difference in the occurrence of hip fractures between a group of 257 osteoporosis patients of both sexes (mean age 70.1 years) treated with 50 mg/d NaF (estimated fluoride intake: 324 µg/kg bw per day[39]), calcium and vitamin D for 2 years and a group of 209 control patients treated with a variety of non-fluoride regimes during the same period. The administration of 50 mg/d NaF combined with calcium or calcitriol to 35 women (68 years of age) for 12 or 13 months resulted in a hip fracture incidence of 5/35 compared with an incidence of 0/43 in patients administered only calcitriol or a

placebo ($p = 0.015$).[120] In a more recent study, women of median age 68 years who were administered 75 mg/d NaF (estimated fluoride intake: 486 µg/kg bw per day[39]) supplemented with calcium for 4 years experienced significantly ($p < 0.01$) more non-vertebral fractures than controls treated with calcium alone. However, the difference in hip fracture incidence between the two groups was not significant.[121]

Reproductive Toxicity and Teratogenicity

Several researchers have examined the effects of relatively high doses of NaF administered in drinking water or in the diet on reproductive function in experimental animals. In a study in which weanling Swiss-Webster female mice were fed a low-fluoride diet (0.1–0.3 ppm) and administered drinking water containing up to 200 ppm fluoride (approximately 40 mg/kg bw per day from drinking water) for 5 weeks prior to and during breeding, maternal growth, survival and litter production were reduced or inhibited.[122] A multigeneration mouse study showed no significant difference in reproductive function for females fed a diet containing <0.5, 2 or 100 ppm fluoride.[123] No pregnancies or embryo implantations were reported in groups of Swiss albino mice orally dosed with fluoride at either 5.2 or 17.3 mg/kg bw per day on days 6–15 after mating.[124] Male rabbits fed NaF at doses of 20 or 40 mg/kg bw per day for 30 days had decreased body weights and significantly lowered sperm motility, sperm counts and fertility rates.[125] Similarly, male Swiss mice fed NaF at doses of 10 or 20 mg/kg bw per day for 30 days exhibited sperm abnormalities, significantly decreased sperm motility and counts and a loss of fertility.[126] In a study in which male and female pastel mink were exposed for 7 months to a diet containing 35 ppm fluoride supplemented with additional fluoride in doses ranging from 33 to 350 ppm, survival was reduced in offspring from dams fed the highest dose of supplemental fluoride, and body weights were increased in offspring of dams receiving 60 and 108 ppm fluoride; litter sizes and gestation periods were not altered by supplemental fluoride.[127]

The oral administration (oral dosing or administration in drinking water) of fluoride at approximately 4.5–200 mg/kg bw per day has also been reported to produce a number of adverse effects on reproductive organs, including a cessation of spermatogenesis and decreases in sperm in the vas deferens and the density of epididymal epithelial cilia in rabbits,[128] increases in seminal vesicle and prostate weights and decreases in the height of the testicular germinal epithelial cells and the cauda and caput epididymis epithelial cells in mice[129,130] and an absence of spermatocyte maturation and degeneration and necrosis of the testicular tubules in mice.[131]

Human studies of the reproductive and developmental effects of ingested fluoride have included a number of case–control and ecological studies examining possible associations between exposure to fluoridated drinking water or fluoride supplements during pregnancy and adverse effects on reproductive function or foetal development. In three case–control studies, no associations were found between fluoride intake and increases in spontaneous abortions,[132] congenital cardiac disease[133] or late adverse pregnancy outcomes, including congenital anomalies, stillbirths and deaths.[134] A recent ecological study that examined total annual fertility rate (TFR) in women aged 10–49 years from 30 regions of the United States reported that twice as many regions containing counties with at least 3 ppm fluoride in their drinking water showed significant negative associations between TFR and fluoride exposure as positive associations. Although meta-analysis of the region-specific results gave a combined negative TFR/exposure association, the authors cautioned that the measures of exposure and outcome may differ between individual women and that the occurrence of significant positive TFR/exposure associations in some regions indicates the possibility of confounding by unknown factors.[135] In a clinical study, children from mothers who had been exposed to fluoridated drinking water and had received a fluoride supplement (1 mg/d) during pregnancy ($n = 117$) were found to be slightly but significantly heavier and longer at birth and suffered from fewer birth defects than those whose mothers had consumed fluoridated water but had received no supplement ($n = 375$).[136]

Genotoxicity

Fluoride (as NaF) has generally given negative results in gene mutation assays using *Escherichia coli* WP2 *hcr*[137] and various strains of *Salmonella typhimurium*.[88,137–141] In addition, NaF was not mutagenic and did not induce gene conversion or aneuploidy in *Saccharomyces cerevisiae* D4.[141,142] NaF induced the "morphological transformation" of Syrian hamster embryo cells *in vitro*, but only at cytotoxic concentrations.[143–146] NaF and potassium fluoride (KF) increased the frequency of gene locus mutations in cultured mammalian[147–149] and human cell lines.[149,150] The preferential increases in "small mutant colonies"[147,148] and negative results obtained for the ouabain locus[147] in these studies are believed to indicate a mechanism based on chromosomal damage rather than point mutations.[39,151] Also, the negative results observed with sodium chloride (NaCl) and potassium chloride (KCl) controls[147,148] suggest that the genotoxic effects are due to a specific effect of the fluoride ion rather than the cations.[39] Although NaF increased unscheduled DNA synthesis in Syrian hamster embryo cells, human foreskin fibroblasts, human keratinocytes[143,152,153] and rat hepatocytes,[154] these results were not confirmed using more rigorous methods of quantifying DNA repair synthesis.[39,138,154,155]

Although NaF has generally demonstrated clastogenic activity (primarily breaks, deletions and gaps with few exchanges) in chromosomal aberration assays using a variety of mammalian and human cell lines, some inconsistencies have been observed.[39,156–158] Inconsistent results have also been reported for *in vitro* sister chromatid exchange assays in human peripheral blood lymphocytes,[138,159,160] Chinese hamster ovary cells[88,138,161] and Syrian hamster embryo cells.[143] NaF exposure increased micronuclei formation in human foreskin fibroblasts[157] and Chinese hamster lung cells.[162] Based on the *in vitro* test results, it has been suggested that fluoride-induced clastogenicity involves the inhibition of DNA synthesis and/or repair and has a threshold concentration of approximately 10 µg/L.[39]

High dietary concentrations of NaF or SnF_2 have been shown to induce recessive lethal mutations in male *Drosophila melanogaster*.[163,164] In most *in vivo* studies with rodents, oral administration of NaF produced no significant effects on the frequency of sister chromatid exchange[161,165,166] or DNA strand breaks [85] or on the incidences of chromosomal aberrations,[141,167] bone marrow micronuclei[140,168–170] or abnormal sperm.[169,171] However, the increased incidences of the latter three end points generally observed following intraperitoneal injection of NaF[172–174] may indicate differential toxicity based on route of administration.[39]

Carcinogenicity

In 1990, the NTP completed a comprehensive study on the carcinogenicity of NaF administered in drinking water (0, 25, 100 or 175 ppm) to male and female F344/N rats and $B6C3F_1$ mice.[88] Osteosarcomas were not induced in the female F344/N rats; in male rats, the incidence was 0/80, 0/51, 1/50 and 3/80 for the four respective dose groups. The incidence in the high-dose male rats was not significantly different from the control group incidence ($p = 0.099$), although a significant dose–response trend was observed ($p = 0.027$). One high-dose male had a subcutaneous osteosarcoma, but no primary bone tumour; although this tumour increased the significance of the trend test ($p = 0.010$), the pairwise comparison with controls remained non-significant ($p = 0.057$). Although the incidence in the high-dose male rats was significantly higher than the average rate for male control rats in the NTP historical data base, the investigators concluded that it was more appropriate to use concurrent controls for comparison purposes because more extensive gross and histopathological examinations of bone and other tissues were made in the current study and because the fluoride content of the standard diet used in the older studies (28–47 ppm) was equivalent to a total fluoride intake between the low- and medium-dose groups in the current study. No other observed tumours (squamous cell neoplasms of the oral mucosa, thyroid gland follicular cell neoplasms, hepatoblastoma, malignant lymphoma) in mice or rats were considered to be significant by the NTP investigators. Based on the study results, the NTP concluded that there was “equivocal evidence of carcinogenic activity” (defined as a marginal increase in neoplasms that may be related to chemical administration) of NaF in male F344/N rats, but no evidence of carcinogenic activity in female F344/N rats or male or female $B6C3F_1$ mice.[88]

In another carcinogenicity bioassay, Sprague-Dawley rats and CD-1 mice received NaF in doses of 0, 4, 10 or 25 mg/kg bw per day in the diet for 95–99 weeks.[89,90] The incidences of bone tumours (chordoma, chondroma, fibroblastic sarcoma and osteosarcoma) in rats (0/70, 0/58, 2/70 and 1/70 for the males and 0/70, 2/52, 0/70 and 0/70 for the females) were not statistically significant compared with controls. Osteomas were found to occur with a statistically significant dose–response trend in both the male and female mice (2/50, 0/42, 5/44 and 26/50 for males and 4/50, 10/42, 5/44 and 26/50 for females), and statistically significant increases were observed for high-dose males and females compared with controls. However, after reviewing the osteoma data, the U.S. Armed Forces Institute of Pathology commented that none of these tumours advanced beyond the benign state or showed pre-cancerous morphology, many were multicentric (i.e., most primary bone cancers are unicentric) and a human counterpart to this type of tumour is not known.[175] The U.S. Food and Drug Administration examined the results of the study, noted a number of problems affecting the interpretation of the results (e.g., high levels of minerals, ions and vitamins in the diet and water; inappropriate dose determination in the preliminary studies; low survival rate for experimental animals and infection of the mice with a retrovirus) and concluded that “under the conditions of the studies, malignant tumours related to dietary fluoride exposure in rodents were not observed.”[8]

Since the introduction of water fluoridation to North America in the 1950s, more than 50 epidemiological studies have been conducted to examine possible associations between the ingestion of fluoridated drinking water and the occurrence of human cancer.[8] One of the more recent studies was a time trend analysis by Freni and Gaylor,[176] which examined the change in cumulative risk of bone cancer for persons 10–29 or 0–74 years of age in 1958–1987 in fluoridated (i.e., fluoride in drinking water serving at least 50% of the population increased to 1 mg/L during or before 1960) versus non-fluoridated areas of the United States, Canada and Europe. The mean change with time in the cumulative bone cancer risk was not significantly different for fluoridated versus non-fluoridated areas.[176] Hoover *et al.*[177] analysed fluoridated counties (i.e., percentage of population receiving fluoridated water increased from <10% to >60% within a 3-year period) compared with control counties (i.e., <10% of population exposed to

fluoridated water) from two National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER) Program registries (Iowa and Seattle, Washington) for the occurrence of cancer and cancer mortality in Caucasians. The observed incidences of osteosarcoma (91 cases), generalized bone and joint cancer (290 cases), cancer of the oral cavity (2693 cases) and renal cancers (2583 cases) in the fluoridated counties were compared with the expected incidences in the control counties. No consistent differences in the observed versus expected cases were noted for any of the cancer types. There was a significant trend ($p = 0.04$) towards increased risk of renal cancer for both sexes combined as the duration of water fluoridation increased from <5 to 15–19 years in the Seattle area (i.e., the relative risk increased from 0.9 [95% CI = 0.7–1.1] to 1.0 [95% CI = 0.9–1.2]). However, no significant trends were observed when males and females were analysed separately or when the data were broken down according to diagnoses made from 1973 to 1980 and from 1981 to 1987.[177,178]

An examination of the entire NCI SEER incidence data base showed that for all ages combined, the incidence of osteosarcoma increased 18% in males and decreased 11% in females between the above two periods. For males <20 years of age in fluoridated communities, the incidence rate of osteosarcoma increased 53% between 1973 and 1980 (88 cases) and between 1980 and 1987 (100 cases), but further analyses showed that the increase was not related to the duration of water fluoridation.[177,178] Hoover *et al.*[177,178] also recently analysed information on more than 2.3 million U.S. cancer deaths occurring between 1950 and 1985 and found no consistent association between exposure to fluoridated drinking water (i.e., counties >50% urbanized in 1980 where the proportion of the population receiving water containing >0.3 ppm fluoride increased from <10% to >66% within a 3-year period) and deaths due to any type of cancer.

These epidemiological studies are of the ecological or geographical correlation type, which suffer from a number of weaknesses, including variations in fluoride intake, geographical differences in variable factors affecting the occurrence of cancer, migration between areas and variations in the quality of mortality and morbidity data.[8,39,109] Although it is generally accepted that ecological studies cannot provide conclusive proof for or against causality, the U.S. Department of Health and Human Services noted that "most epidemiologists consider studies of geographic correlations valuable in indicating the likelihood that positive links do or do not exist or in demonstrating the feasibility of hypotheses."[8] Many of these studies were reviewed by three major working groups (i.e, the British Working Party on the Fluoridation of Water and Cancer, the International Agency for Research on Cancer and the U.S. National Academy of Sciences), and all three concluded that the available body of evidence shows no consistent association between the consumption of fluoridated drinking water and the risk of cancer morbidity or mortality.[109,179,180]

Dental Effects

Dental fluorosis is a permanent hypomineralization of tooth enamel due to a fluoride-induced disruption of tooth development.[181–184] In the mildest forms, only the outermost layer of enamel is affected, producing diffuse white lines across the tooth surface.[182] As the severity increases, deeper layers are affected and the porosity increases, leading to a chalky white appearance.[175,182] Eventually, chewing and other forces erode the surface enamel, producing pits that can become stained by various food constituents.[182]

Generally, the milder forms of dental fluorosis do not alter tooth function and are considered to represent an aesthetic rather than a health effect,[8] although significant enamel erosion could lead to tooth pain and impairment of chewing ability and require complex restorative procedures.[175]

Epidemiological studies of various age cohorts of children exposed to different fluoride concentrations in drinking water have identified the later maturation stage rather than the earlier secretory stage as the period of enamel development most sensitive to the occurrence of dental fluorosis.[181] As the milder forms of dental fluorosis are the ones most often seen in North America,[185] the anterior teeth, particularly the maxillary central incisors (MCI), are believed to be the most important ones for judging the risk of dental fluorosis.[181,175,186] An analysis of small groups of Hong Kong school children before and after a reduction in the fluoride concentration in the community drinking water supply concluded that there is a minimal risk to the MCI before 18 months of age, but 22–26 months of age represents the period of greatest risk.[187] After tooth development is complete (i.e., 5–6 years of age for the MCI), there is no longer a risk of dental fluorosis.[32,186,187]

An Advisory Review Panel of dental researchers recently examined the available data on the relationship between total daily fluoride intake and the prevalence of dental caries and dental fluorosis in children.[188] The data reviewed ranged from the studies of Dean *et al.*,[189,190] conducted in the 1940s with children 12–14 years of age who were lifelong residents of 21 U.S. communities and whose drinking water contained naturally occurring fluoride, to more modern studies using children of various ages from fluoridated and non-fluoridated communities in Canada, the United States, Australia and other countries.[191,192] The critical studies for defining the dose–response relationship between total daily fluoride intake and dental caries/fluorosis were found to be those of Dean *et al.*,[189,190] supplemented with data compiled in

1958 on 12- to 14-year-old children from 20 U.S. communities.[193] The panel concluded that these older dose–response studies were more applicable than modern ones because the age ranges of the children in the modern studies varied; the modern studies have relatively few data on dental fluorosis and caries prevalence in communities with fluoride concentrations in drinking water below 1.0 ppm; and most of the modern studies have not accounted for the confounding effect of sources of fluoride that were not available in the 1940s (e.g., toothpaste, mouth rinses, gels).[188]

With respect to the occurrence of dental fluorosis, analysis of the original data of Dean *et al.*[189,190] showed that 1940s children consuming drinking water containing ≤1.6 ppm fluoride experienced low rates of very mild (22%) and mild (4%) dental fluorosis, but no moderate or severe dental fluorosis. The total daily fluoride intake for these children (i.e., from air, soil, food and water) can be considered to represent the maximum daily fluoride intake that is unlikely to result in moderate to severe dental fluorosis.

The maximum daily fluoride intake can be estimated from modern data (Table 1) if it is assumed that the daily fluoride intakes from air, soil and food have not changed significantly since the 1940s and the daily drinking water consumption (i.e., number of litres per day) has remained relatively constant.* Using the 7 month to 4 year age group (Table 1) as a surrogate for the period of greatest risk of dental fluorosis (22–26 months of age), the estimated maximum daily fluoride intake is the sum of the maximum daily intakes from air (0.01 µg/kg bw per day), soil (1.19 µg/kg bw per day), food (22.3 µg/kg bw per day) and drinking water (0.8 L/day × 1.6 mg/L[189,190] ÷13 kg bw = 98.5 µg/kg bw per day), which is 122 µg/kg bw per day.

Dental caries result from the localized dissolution of tooth enamel by acids produced by bacterial deposits (plaque). The period of greatest susceptibility to caries is believed to extend from the time teeth first emerge to full eruption for both the primary and permanent dentition.[195] Initially, the ability of fluoride to prevent the formation of clinically detectable caries was thought to be primarily due to pre-eruptive incorporation, producing improved crystal stability and reduced enamel solubility.[196,197] Fluoride was also shown to inhibit plaque bacterial acid production.[198] However, reviews of clinical studies of water fluoridation and fluoride's effects on mineralization indicate that fluoride's major anticariogenic effect is post-eruptive, through the inhibition of demineralization and the enhancement of remineralization of early caries lesions.[195,197] Consistent with this post-eruptive mechanism are observations of significantly less decayed and filled tooth surfaces in adults exposed to fluoridated drinking water from ages 15 to 34[198] and significantly lower coronal and root caries incidences for adults >65 years of age residing in fluoridated communities for at least 30–40 years compared with lifelong residents of non-fluoridated communities.[199]

The dose–response data of Dean *et al.*[189,190] and Eklund and Striffler[193] suggest a relatively small decline in dental caries incidence in 12- to 14-year-olds when fluoride concentrations in drinking water increased from 0.8 to 1.2 ppm compared with much larger declines for fluoride concentrations below 0.8 ppm. This decrease in the slopes of the dose–response curves and the fact that Dean *et al.*[189,190] observed the occurrence of only the very mild to mild forms of dental fluorosis at concentrations of 0.8–1.2 ppm led the Advisory Review Panel[188] to select this range as an optimal range of fluoride concentrations. The panel concluded that at the time of Dean *et al.*'s[189,190] research, children who consumed drinking water containing 0.8–1.2 ppm fluoride combined with intakes of fluoride from air, food and soil were obtaining an optimal daily fluoride intake for the prevention of dental caries.[188] However, as fluoride prevents dental caries through both pre- and post-eruptive mechanisms[195–197] in children and adults,[198,199] it is likely that there is a relatively wide range of optimal daily fluoride intakes, depending on the age group considered.

Classification and Assessment

The existing epidemiological studies do not support an association between cancer morbidity or mortality and the consumption of fluoridated drinking water. However, as virtually all of these studies are of the ecological or geographical correlation type, their limitations preclude them from providing conclusive evidence for or against an exposure–response relationship. At the same time, ecological studies can be useful for testing the feasibility of hypotheses, and several reviews have noted that the consistency of these studies in not showing a positive association between exposure to fluoridated drinking water and cancer morbidity or mortality can impart a degree of confidence in their findings.

A comprehensive bioassay sponsored by the NTP[88] provided limited evidence for the carcinogenicity of fluoride based on the observation of a significant dose–response trend for the occurrence of osteosarcomas in

* The approach followed for the derivation of the maximum daily fluoride intake was a modification of the approach described by the Advisory Review Panel in reference 188. Estimates of daily fluoride intake from air and soil and daily drinking water consumption for Canadian children in the 1940s were not identified. The only available 1940s-era estimate of children's daily fluoride intake from food[194] was not used in the determination of the maximum daily fluoride intake because it relied on standardized calorie allotments, estimated food energy values and estimated ranges of fluoride concentrations in food rather than dietary recall surveys and analysis of the specific food groups consumed for their fluoride content.

male F344/N rats consuming drinking water containing 25–175 ppm NaF. However, a pairwise comparison of osteosarcoma incidence in the high-dose versus control males was not significant, and no dose–response trend for the occurrence of osteosarcoma was observed in female rats or male and female B6C3F$_1$ mice exposed to the same concentrations of fluoride in drinking water. A carcinogenicity bioassay in which male and female Sprague-Dawley rats and CD-1 mice were administered NaF at doses of 4–25 mg/kg bw per day in the diet found no statistically significant dose–response relationship for osteosarcomas in either sex of both species.[89,90] However, recent reviews have noted several limitations of this second bioassay, including high levels of minerals, ions and vitamins in the diet and drinking water; poor survival rate, leading to an early termination of the study; and infection of the mice with a retrovirus.

NaF is capable of inducing clastogenic effects in mammalian cells *in vitro*, mutations in *D. melanogaster in vivo* and clastogenicity and other genotoxic effects when administered by intraperitoneal injection to rodents. However, fluoride generally did not increase chromosomal aberrations, micronuclei formation, sister chromatid exchange or DNA strand breaks when administered orally to rodents. It has been suggested that fluoride-induced genotoxicity involves an inhibition of the synthesis of proteins essential for DNA synthesis/repair rather than a direct interaction between fluoride and DNA.

Following a comprehensive review of the available data on the carcinogenicity and genotoxicity of inorganic fluoride, the *Canadian Environmental Protection Act* (CEPA) Priority Substances assessment of inorganic fluoride concluded that "although there is some evidence for the carcinogenicity of inorganic fluoride, available data [i.e., laboratory and epidemiological data] are inconclusive."[39] Based on this conclusion and a consideration of the principles and approaches for the derivation of maximum acceptable concentrations (MACs) for chemicals in Canadian drinking water, it was determined that a tolerable daily intake (TDI) for fluoride should be derived by division of a NOAEL, lowest-observed-adverse-effect level (LOAEL) or other suitable effect level for a significant non-neoplastic effect by an appropriate uncertainty factor.

Because of the availability of data from human studies and interspecies differences (especially rats) in the response to fluoride exposures, the CEPA assessment emphasized human studies in the development of a daily intake level above which non-neoplastic adverse effects are expected to occur.[4] The conclusion of the CEPA assessment regarding the health effects data for inorganic fluoride was that "potentially adverse effects associated with skeletal fluorosis are likely to be observed at intakes greater than approximately 200 µg/kg bw per day fluoride."[39] Some of the evidence supporting this intake level included a small number of case reports of crippling skeletal fluorosis following fluoride intakes of approximately 215–285 µg/kg bw per day and the observation of stage I skeletal fluorosis in osteoporosis patients treated with fluoride at doses of 260–389 µg/kg bw per day. Osteoporosis patients were also reported to have small increases in hip fracture incidence following treatment with doses of fluoride greater than or equal to approximately 260 µg/kg bw per day. Also, the 200 µg/kg bw per day effect level is within the range of daily intakes predicted (i.e., based on modelling) to result in bone fluoride concentrations associated with adverse skeletal effects in humans.[4]

An Advisory Review Panel of dental researchers recently reviewed the available data on the relationship between daily fluoride intake in childhood and the occurrence of dental fluorosis. Based on the conclusions of this review[188] and data on the period of greatest risk for dental fluorosis in the anterior permanent teeth, it was estimated that a daily fluoride intake less than or equal to 122 µg/kg bw per day for children 22–26 months old (i.e., period of greatest risk) is unlikely to result in moderate to severe dental fluorosis in the anterior permanent teeth.

The TDI for fluoride is considered to be 122 µg/kg bw per day (0.122 mg/kg bw per day), the daily fluoride intake that is unlikely to produce moderate to severe dental fluorosis in children 22–26 months old. No uncertainty factor was applied in the derivation of the TDI, because the daily intake level was based on studies of the most susceptible age group in the human population. Although there is some controversy as to whether the more severe forms of dental fluorosis represent an aesthetic or a health effect, a limited number of surveys have shown that lay people can detect dental fluorosis, and both clinicians and lay people view the more severe forms as socially embarrassing to the children afflicted.[200–202] As the TDI is 40% less than the 200 µg/kg bw per day effect level for skeletal fluorosis, daily fluoride intakes less than or equal to the TDI are unlikely to produce adverse effects associated with skeletal fluorosis.

Rationale

A MAC for fluoride could be derived from the TDI as follows:

$$\text{MAC} = \frac{0.122 \text{ mg/kg bw per day} \times 13 \text{ kg bw} \times 0.50}{0.8 \text{ L/d}} \approx 1.0 \text{ mg/L}$$

where:

0.122 mg/kg bw per day is the TDI, as described above
13 kg bw is the average body weight for a child in the 7 month to 4 year age group (age group from the CEPA assessment encompassing the period of greatest risk for dental fluorosis)[40]
0.50 is the average proportion of total daily fluoride intake allocated to drinking water for children in the 7 month to 4 year age group residing in fluoridated communities in Canada (Table 1)
0.8 L/d is the average daily water consumption for a child in the 7 month to 4 year age group.[40]

After reviewing the proposed drinking water guideline, the Federal–Provincial Subcommittee on Drinking Water concurred with the approaches used for the derivation of both the TDI and the proposed MAC. However, the subcommittee members had two major concerns regarding the proposed MAC: the age of the studies used to estimate daily fluoride intakes from various sources, and the apparent absence of a tangible health benefit associated with reducing the MAC to 1.0 mg/L from the current level of 1.5 mg/L.*

Because most of the studies used to estimate daily fluoride intake were conducted between 1970 and 1990, the subcommittee questioned whether these studies reflect current trends in fluoride intake for Canadian children. This is especially the case for intakes from sources other than drinking water (e.g., toothpaste ingestion). In the early 1990s, dental researchers began to advocate measures to reduce children's fluoride intake from toothpaste ingestion, such as adult supervision of tooth brushing, use of a pea-sized amount of toothpaste, discouraging the swallowing of toothpaste, etc.[36] These recommendations may have already reduced the daily intake of fluoride for many Canadian children below the estimated levels used in the derivation of the proposed MAC.

A reduction in the MAC from 1.5 mg/L to 1.0 mg/L would not be expected to significantly decrease the risk of fluoride-induced health effects. Even for communities where the concentration of fluoride in drinking water is 1.5 mg/L, the total daily fluoride intake is estimated to be below the 200 µg/kg bw per day effect level for skeletal fluorosis. In the absence of a significant reduction in health risk, the subcommittee concluded that the increased water treatment costs that would have to be incurred by those communities and private wells that exceed a lowered guideline would be excessive.

Consequently, the subcommittee recommended that the MAC for fluoride be maintained at 1.5 mg/L. The subcommittee also encouraged efforts to control fluoride intake from sources such as toothpaste ingestion and efforts to obtain more up-to-date estimates of daily fluoride intake in Canada. Although drinking water supplies containing fluoride at concentrations above the MAC do not necessarily represent a risk to human health, a risk of moderate to severe dental fluorosis could seriously affect the acceptance of drinking water supplies by consumers and should be avoided.

Although elucidated over 50 years ago, the caries preventative effects of fluoridated drinking water are still evident in modern studies of fluoridated versus non-fluoridated communities. The caries preventative effects arise primarily through a post-eruptive mechanism and have been demonstrated not only in children, but in adults as well. Although the effectiveness of water fluoridation may have decreased over time, this has been attributed to other sources of fluoride (e.g., toothpaste and other fluoridated dental products) that have become available in both fluoridated and non-fluoridated communities since the time of the original research on water fluoridation. Numerous dental and public health associations and dental researchers consider water fluoridation to be a cornerstone method for caries prevention available to all those on public water supplies, regardless of socio-economic status or level of dental care.

If it is desired that water supplies be fluoridated as a public health measure for the prevention of dental caries, an optimal fluoride concentration of 0.8–1.0 mg/L should be maintained. The consumption of drinking water containing 0.8–1.0 mg/L fluoride combined with average daily fluoride intakes from other sources to which Canadian consumers are commonly exposed should convey the beneficial dental effects of fluoride to all age groups. This optimal concentration range was selected by the subcommittee based on a careful consideration of both the MAC and the Advisory Review Panel's recommendations regarding optimal fluoride concentrations.

It is apparent from the data in Table 1 that some children who consume drinking water containing 0.8–1.0 mg/L fluoride may have total daily fluoride intakes that exceed the TDI. However, in recommending this optimal concentration range, the subcommittee recognized concerns similar to those that led to the rejection of the proposed MAC — i.e., available estimates of total daily fluoride intake by Canadian children may not reflect current intake patterns because of recent initiatives to control fluoride intake from toothpaste ingestion, and the selection of a lower optimal concentration range would not significantly reduce the risk of fluoride-induced health effects, but would reduce the beneficial effects of fluoridated drinking water.

The daily intake of drinking water containing fluoride at or below the MAC combined with average daily intakes of fluoride from air, soil, food and toothpaste should not result in adverse effects associated with skeletal fluorosis. However, the CEPA assessment compared the "estimated daily intakes with those to which it is believed that a person can be exposed daily over a lifetime without developing deleterious non-neoplastic effects" and found that "these average daily intakes are at least 20% less than the level at which adverse effects upon the skeleton ... are anticipated."[4] In view of this small difference, the CEPA assessment recommended "that exposure of the population of Canada to inorganic fluorides continue to be closely monitored."[4]

If the reference values for the 20+ year age group (i.e., body weight, proportional allocation of drinking water to daily fluoride intake, daily water

* The sixth edition of the *Guidelines for Canadian Drinking Water Quality* lists a MAC of 1.5 mg/L for fluoride.[203] This MAC was originally established in 1978.[204]

consumption)* are applied to the 200 µg/kg bw per day effect level for skeletal fluorosis, a reference concentration of 3.7 mg/L can be derived. This reference concentration should under no circumstances supersede or replace the MAC, but it could serve as a useful guide for addressing possible concerns over the relationship between fluoride intake from drinking water and the occurrence of skeletal fluorosis.

References

1. Cotton, F.A. and Wilkinson, G. Advanced inorganic chemistry. John Wiley & Sons, New York, NY. p. 546 (1988).

2. Mackay, K.M. and Mackay, R.A. Introduction to modern inorganic chemistry. 4th edition. Prentice Hall, Englewood Cliffs, NJ. p. 339 (1989).

3. Canadian Public Health Association. Fluoride in the environment. Chapter 3 in: Criteria document in support of a drinking water standard for fluoride. Final report. Ottawa (1979).

4. Environment Canada and Health Canada. Inorganic fluorides. Priority substances list assessment report. DSS Catalogue No. En 40-215/32E, Supply and Services Canada, Ottawa (1993).

5. Budavari, S. (ed.). The Merck Index: an encyclopedia of chemicals, drugs, and biologicals. 11th edition. Merck & Co., Rahway, NJ. p. 8565 (1989).

6. Reeves, T.G. Water fluoridation. Chapter 15 in: Water quality and treatment. 4th edition. F.W. Pontius (ed.). McGraw-Hill, New York, NY (1990).

7. Ripa, L.W. Fluorides. Chapter 6 in: Preventive dental services. 2nd edition. Department of National Health and Welfare, Ottawa (1988).

8. Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Review of fluoride benefits and risks. Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC, February (1991).

9. Symonds, R.B., Rose, W.I. and Reed, M.H. Contribution of Cl- and F-bearing gases to the atmosphere by volcanoes. Nature, 334: 415–418 (1988), cited in reference 4.

10. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for fluorides, hydrogen fluoride, and fluorine (F). ATSDR/TP-91/17, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA, April (1993).

11. World Health Organization. Fluorine and fluorides. Environmental Health Criteria 36, International Programme on Chemical Safety, Geneva (1984).

12. Department of National Health and Welfare, Yukon Territory. Chemical water analysis relative to surface and drinking waters in the Yukon Territory from the year 1986 to 1989. Provided by G.W. Allen, Environmental Health Division, Medical Services Branch (1989), cited in reference 39.

13. Environment Canada (Atlantic Region). Federal–provincial toxic chemical survey of municipal drinking water sources. Data summary report. Province of Prince Edward Island 1986–1988. Report IWD-AR-WQB-89-156, Water Quality Branch, Inland Waters Directorate, Environment Canada, Moncton, NB (1989), cited in reference 39.

14. Greater Vancouver Regional Water District. 1989 summary of chemical and physical analysis for the Seymour, Capilano and Coquitlam water supplies. Provided by G.T. Marsh, Burnaby, B.C. (1990), cited in reference 39.

15. Droste, R.L. Fluoridation in Canada as of December 31, 1986. Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, June (1987).

16. Quebec Ministry of the Environment. Personal communication with S. Théberge concerning Quebec municipalities that fluoridate drinking water and the levels of fluoride found in January 1989 (1990), cited in reference 39.

17. Ontario Ministry of the Environment. 1989. Drinking Water Surveillance Program (DWSP) results of fluoride in raw and treated waters. Printout provided by P. Lachmaniuk, Water Resources Branch (1990), cited in reference 39.

18. Alberta Environment. Fluoride summary 1989 — Composite community data. Printout provided by G.P. Halina, Municipal Branch, Standards and Approvals Division, Environmental Protection Services (1990), cited in reference 39.

19. Dabeka, R.W. and McKenzie, A.D. Personal communication (1993), cited in reference 39.

20. Taves, D.R. Dietary intake of fluoride ashed (total fluoride) v. unashed (inorganic fluoride) analysis of individual foods. Br. J. Nutr., 49: 295–301 (1983), cited in reference 39.

21. Dabeka, R.W., Conacher, B.S., Salminen, J., Nixon, G.R., Riedel, G., Crocker, R. and Dubé, G. Survey of bottled drinking water sold in Canada. Part I. Lead, cadmium, arsenic, aluminum, and fluoride. J. Assoc. Off. Anal. Chem. Int., 75: 949–953 (1992).

22. Marier, J.R. Intakes of magnesium and fluoride, and some systemic effects. Proc. Finn. Dent. Soc., 87: 581–594 (1991), cited in reference 39.

23. Schamschula, R.G., Un, P.S., Sugar, E. and Duppenthaler, J.L. The fluoride content of selected foods in relation to the fluoride concentration of water. Acta Physiol. Hung., 72: 217–227 (1988), cited in reference 39.

24. Kumpulainen, J. and Koivistoinen, P. Fluorine in foods. Residue Rev., 68: 37–57 (1977), cited in reference 39.

25. McKnight-Hanes, M.C., Leverett, D.H., Adair, S.M. and Shields, C.P. Fluoride content of infant formulas: soy-based formulas as potential factor in dental fluorosis. Pediatr. Dent., 10: 189–194 (1988), cited in reference 39.

26. Dabeka, R.W., Karpinski, K.F., McKenzie, A.D. and Bajdik, C.D. Survey of lead, cadmium and fluoride in human milk and correlation of levels with environmental and food factors. Food Chem. Toxicol., 24: 913–921 (1986), cited in reference 39.

27. McGrath, T.M. Assessment of fluoride exposure in populations residing close to fluoride emitting brick plants. Special Studies and Services Branch, Ontario Ministry of Labour, Toronto (1983), cited in reference 39.

28. Sidhu, S.S. Fluoride deposition through precipitation and leaf litter in a boreal forest in the vicinity of a phosphorus plant. Sci. Total Environ., 23: 205–214 (1982), cited in reference 39.

29. Schuppli, P.A. Total fluorine in CSSC reference soil samples. Can. J. Soil Sci., 65: 605–607 (1985), cited in reference 39.

* For the 20+ year age group, the average body weight was assumed to be 70 kg,[40] the proportion of total daily intake allocated to drinking water was 0.40 (Table 1) and the average daily water consumption was assumed to be 1.5 L.[40]

30. Newbrun, E. Current regulations and recommendations concerning water fluoridation, fluoride supplements, and topical fluoride agents. J. Dent. Res., 71: 1255–1265 (1992).

31. Stookey, G.K. Review of benefits vs. fluorosis risk of self-applied topical fluorides (dentrifices, mouthrinses, gels). Presented at the Canadian Workshop on the Evaluation of Current Recommendations Concerning Fluorides, Toronto, April 9–11 (1992).

32. Stookey, G.K. Review of fluorosis risk of self-applied topical fluorides — dentrifice, mouthrinses, and gels. Community Dent. Oral Epidemiol., 22(3): 181–186 (1994).

33. Burgess, R.C. Fluoride ingestion from dental products. In: Investigation of inorganic fluoride and its effects on the occurrence of dental caries and dental fluorosis in Canada. Report prepared for the Department of National Health and Welfare under Research Contract No. 3726 (1993).

34. Beltran, E.D. and Szpunar, S.M. Fluoride in toothpaste for children: suggestions for change. Pediatr. Dent., 3: 185–188 (1988), cited in reference 33.

35. Levy, S.M. A review of fluoride intake from fluoride dentrifice. J. Dent. Child., 60: 115–124 (1993).

36. Clark, D.C. Appropriate uses of fluorides for children: guidelines from the Canadian Workshop on the Evaluation of Current Recommendations Concerning Fluorides. Can. Med. Assoc. J., 149(12): 1787–1793 (1993).

37. Canadian Paediatric Society, Nutrition Committee. Fluoride supplementation. Canadian Paediatric Society Statement: N 86-01. Ottawa (1986).

38. McFarlane, D.J. (former Senior Dental Consultant, Ontario Ministry of Health). Personal communication (1993), cited in reference 33.

39. Department of National Health and Welfare. Inorganic fluorides. Unpublished supporting documentation, health-related sections, for priority substances assessment report (1993).

40. Health Canada. *Canadian Environmental Protection Act.* Human health risk assessment for priority substances. DSS Catalogue No. En 40-215/41E, Supply and Services Canada, Ottawa (1994).

41. Whitford, G.M., Allman, D.W. and Shahed, A.R. Topical fluorides: effects on physiologic and biochemical process. J. Dent. Res., 66: 1072–1078 (1987), cited in reference 33.

42. Greenberg, A.E., Clesceri, L.S. and Eaton, A.D. (eds.). Standard methods for the examination of water and wastewater. 18th edition. American Public Health Association, American Water Works Association and Water Environment Federation, Washington, DC (1992).

43. Leung, D.C.W. and Hrudey, S.E. Removal of fluorides from water supplies. Report prepared for Standards and Approvals Division, Municipal Engineering Branch, Alberta Environment, July (1985).

44. Department of National Health and Welfare. Guidelines for Canadian drinking water quality. Water treatment principles and applications. A manual for the production of drinking water. Prepared by Environmental Health Directorate, Health Protection Branch; printed by Canadian Water and Wastewater Association, Ottawa (1993).

45. Ontario Ministry of the Environment. De-fluoridation of potable water. Unpublished report, Water Resources Branch, Toronto (1992).

46. Tillman, G.M. Water fluoridation. Operator's guide series. Lewis Publishers, Boca Raton, FL (1993).

47. Department of National Health and Welfare. Recommended nutrient intakes for Canadians. Health Protection Branch, Ottawa (1983).

48. Department of National Health and Welfare. Nutrition recommendations. The report of the Scientific Review Committee. Supply and Services Canada, Ottawa. p. 160 (1990).

49. U.S. National Research Council, Food and Nutrition Board. Recommended dietary allowances. 10th edition. National Academy Press, Washington, DC (1989), cited in reference 181.

50. Ekstrand, J. Pharmacokinetic aspects of topical fluorides. J. Dent. Res., 66: 1061–1065 (1987), cited in reference 39.

51. Ekstrand, J. and Ehrnebo, M. Influence of milk products on fluoride bioavailability in man. Eur. J. Clin. Pharmacol., 16: 211–215 (1979), cited in reference 39.

52. Sato, T., Yoshitake, K. and Hitomi, G. Mechanisms of fluoride absorption from the gastrointestinal tract in rats. Fluoride Res. 1985; Stud. Environ. Sci., 27: 325–332 (1986), cited in reference 39.

53. Messer, H.H., Nopakum, J. and Rudney, J.D. Influence of pH on intestinal fluoride transport *in vitro*. J. Dent. Assoc. Thai., 39: 226–232 (1989), cited in reference 39.

54. U.S. Environmental Protection Agency. Drinking water criteria document on fluoride. Contract 68-03-3279, Office on Drinking Water, Cincinnati, OH (1985).

55. Spencer, H., Kramer, L., Norris, C. and Wiatrowski, E. Effect of aluminum hydroxide on fluoride metabolism. Clin. Pharmacol. Ther., 28: 529–535 (1980), cited in reference 39.

56. Carlson, C., Armstrong, W. and Singer, L. Distribution and excretion of radiofluoride in the human. Proc. Soc. Exp. Biol. Med., 104: 235–239 (1960), cited in reference 39.

57. Ekstrand, J., Alvan, G., Boreus, L.O. and Norlin, A. Pharmacokinetics of fluoride in man after single and multiple oral doses. Eur. J. Clin. Pharmacol., 12: 311–317 (1977), cited in reference 54.

58. Ekstrand, J., Odont, L. and Ehrnebo, M. The relationship between plasma fluoride, urinary excretion rate and urine fluoride concentration in man. J. Occup. Med., 25: 745–748 (1983), cited in reference 54.

59. McIvor, M.E. Acute fluoride toxicity: pathophysiology and management. Drug Saf., 5: 79–85 (1990), cited in reference 39.

60. Nedeljkovic, M., Matovic, V. and Maksimovic, M. Toxicokinetic studies of fluoride in rabbits. In: Nutrient availability: chemical and biological aspects. D.A. Southgate, I.T. Johnson and G.R. Fenwick (eds.). Royal Society of Chemistry Publication No. 72. pp. 290–292 (1989), cited in reference 39.

61. Hodge, H.C. and Smith, F.A. Biological properties of inorganic fluorides. In: Fluorine chemistry. J.H. Simons (ed.). Academic Press, New York, NY. pp. 1–43 (1965), cited in reference 39.

62. Hamilton, M. Water fluoridation: a risk assessment perspective. J. Environ. Health, 54: 27–32 (1992), cited in reference 39.

63. Kaminsky, L.S., Mahoney, M.C., Leach, J., Melius, J. and Miller, M.J. Fluoride: benefits and risks of exposure. Crit. Rev. Oral Biol. Med., 1: 261–281 (1990), cited in reference 39.

64. Grandjean, P. and Thomsen, G. Reversibility of skeletal fluorosis. Br. J. Ind. Med., 40: 456–461 (1983), cited in reference 39.

65. Grynpas, M.D. Fluoride effects on bone crystals. J. Bone Min. Res., 5: S169–S175 (1990), cited in reference 39.

66. Caraccio, T.P., Greensher, J. and Mofenson, H.C. The toxicology of fluoride. In: Clinical management of poisoning and drug overdose. L. Haddad and J. Winchester (eds.). W.B. Saunders Co., Philadelphia, PA (1983), cited in reference 39.

67. Whitford, G.M. The physiological and toxicological characteristics of fluoride. J. Dent. Res., 69: 539–549 (1990).

68. Hodge, H.C. and Smith, F.A. Minerals: fluorine and dental caries. In: Dietary chemicals vs. dental caries. Advances in Chemistry Series No. 94, American Chemical Society, Washington, DC (1970), cited in reference 39.

69. Weatherell, J.A., Deutsch, D., Robinson, C. and Hallsworth, A.S. Assimilation of fluoride by enamel throughout the life of the tooth. Caries Res., 11 (Suppl. 1): 85–115 (1977), cited in reference 11.

70. Schamschula, R.G., Sugar, E., Agus, H.M., Un, P.S.H. and Toth, K. The fluoride content of human tooth enamel in relation to environmental exposure to fluoride. Aust. Dent. J., 24(4): 243–247 (1982), cited in reference 11.

71. Alhava, E.M., Olkkonen, H., Kauranen, P. and Kari, T. The effect of drinking water fluoridation on the fluoride content, strength and mineral density of human bone. Acta Orthop. Scand., 51: 413–420 (1980), cited in reference 39.

72. Berndt, A.F. and Stearns, R.I. Dental fluoride chemistry. Charles C. Thomas, Springfield, IL (1979), cited in reference 39.

73. U.S. National Academy of Sciences. Fluorides, biologic effects of atmospheric pollutants. Washington, DC (1971).

74. Van Rensburg, B.G. Metabolism of fluorides. Tydskr. Tandheelkd. Ver. S. Afr., 34: 163–166 (1979), cited in reference 8.

75. Ekstrand, J., Hardell, L.I., *et al.* Fluoride balance studies on infants in a 1ppm-water-fluoride area. Caries Res., 18(4): 87–92 (1984), cited in reference 8.

76. Ekstrand, J., Spak, C.J., *et al.* Distribution of fluoride to human breast milk following intake of high doses of fluoride. Caries Res., 18(1): 93–95 (1984), cited in reference 39.

77. Spencer, H., Osis, D. and Lender, M. Studies of fluoride metabolism in man: a review and report of original data. Sci. Total Environ., 17: 1–12 (1981), cited in reference 39.

78. Spencer, H., Lewin, I., Wistrowski, E. and Samachson, J. Fluoride metabolism in man. Am. J. Med., 49: 807–813 (1970), cited in reference 39.

79. Augenstein, W.L., Spoerke, D.G., Kulig, K.W., Hall, A.H., Hall, P.K., Riggs, B.S., Saadi, M.E. and Rumack, B.H. Fluoride ingestion in children: a review of 87 cases. Pediatrics, 88: 907–912 (1991), cited in reference 39.

80. Lim, J.K.J., Jensen, G.K. and King, O.H., Jr. Some toxicological aspects of stannous fluoride after ingestion as a clear, precipitate free solution compared to sodium fluoride. J. Dent. Res., 54: 615–625 (1975), cited in reference 109.

81. Segreto, B.A., Yeary, R.A., Broks, R. and Harris, N.O. Toxicity study of stannous fluoride in Swiss strain mice. J. Dent. Res., 40: 623 (1960), cited in reference 109.

82. Lim, J.K., Renaldo, G.J. and Chapman, P. LD50 of SnF_2, NaF and Na_2PO_3F in the mouse compared to the rat. Caries Res., 12: 177–179 (1978), cited in reference 67.

83. Gruninger, S.E., Clayton, R., Chang, S.-B. and Siew, C. Acute oral toxicity of dentrifice fluorides in rats and mice. J. Dent. Res., 67: 334 (Abstr. No. 1769) (1988), cited in reference 67.

84. DeLopez, O.H., Smith, F.A. and Hodge, H.C. Plasma fluoride concentrations in rats acutely poisoned with sodium fluoride. Toxicol. Appl. Pharmacol., 37: 75–83 (1976), cited in reference 10.

85. Skare, J.A., Schrotel, K.R. and Nixon, G.A. Lack of DNA-strand breaks in rat testicular cells after *in vivo* treatment with sodium fluoride. Mutat. Res., 170: 85–92 (1986), cited in reference 10.

86. Whitford, G.M., Finidori, C. and Birdsong-Whitford, N.L. Acute LD_{50} values of F given as NaF and/or MFP in the rat. Caries Res., 21: 166 (Abstr. No. 22) (1987), cited in reference 67.

87. Shourie, K.L., Hein, J.W. and Hodge, H.C. Preliminary studies of the caries inhibiting potential and acute toxicity of sodium monofluorophosphate. J. Dent. Res., 29: 529–533 (1950), cited in reference 67.

88. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of sodium fluoride (CAS No. 7681-49-4) in F344/N rats and B6C3F_1 mice (drinking water studies). NTP TR 393, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC (1990).

89. Maurer, J.K., Cheng, M.C., Boysen, B.G. and Anderson, R.L. Two-year carcinogenicity study of sodium fluoride in rats. J. Natl. Cancer Inst., 82: 1118–1126 (1990), cited in reference 39.

90. Maurer, J.K., Cheng, M.C., Boysen, B.G., Squire, R.A., Stranberg, J.D., Weisbrode, J.L. and Anderson, R.L. Confounded carcinogenicity study of sodium fluoride in CD-1 mice. Regul. Toxicol. Pharmacol., 18: 154–168 (1993), cited in reference 39.

91. Gruber, H.E. and Baylink, D.J. The effects of fluoride on bone. Clin. Orthop., 267: 264–277 (1991), cited in reference 39.

92. Hodge, H.C. and Smith, F.A. Fluoride. In: Disorders of mineral metabolism. Vol. 1. F. Bonner and J.W. Colburn (eds.). Academic Press, New York, NY. pp. 439–483 (1981), cited in reference 8.

93. Sowers, M., Wallace, R.B. and Lemke, J.H. The relationship of bone mass and fracture history to fluoride and calcium intake: a study of three communities. Am. J. Clin. Nutr., 44: 889–898 (1986), cited in reference 8.

94. Schlesinger, E.R., Overton, D.E., Chase, H.C. and Cantwell, K.T. Newburgh-Kingston caries-fluorine study. XIII. Pediatric findings after ten years. J. Am. Dent. Assoc., 52: 296–306 (1956).

95. McCauley, H.B. and McClure, F.J. Effect of fluoride in drinking water on the osseous development of the hand and wrist in children. Public Health Rep., 69: 671–682 (1954), cited in reference 8.

96. Leone, L.C., Stevenson, C.A., Hilbish, T.F. and Sosman, M.C. A roentgenologic study of a human population exposed to high-fluoride domestic water. Am. J. Roentgenol., 74: 874–885 (1955), cited in reference 39.

97. Stevenson, C.A. and Watson, A.R. Fluoride osteosclerosis. Am. J. Roentgenol., 78: 13–18 (1957), cited in reference 8.

98. Krishnamachari, K.A.V.R. Fluorine. Trace Elem. Hum. Anim. Nutr., 1: 365–415 (1987), cited in reference 39.

99. Royal College of Physicians of London. Fluoride, teeth and health. A report and summary on fluoride and its effects on teeth and health. Pitman Medical, London, UK. p. 85 (1976), cited in reference 39.

100. Singh, A. and Jolly, S.S. Chronic toxic effects on the skeletal system. In: Fluorides and human health. Monograph Series No. 59, World Health Organization. pp. 238–249 (1970).

101. Felsenfeld, A.J. and Roberts, M.A. A report of fluorosis in the United States secondary to drinking well water. J. Am. Med. Assoc., 265: 486–488 (1991).

102. Sauerbrunn, B.J.L., Ryan, C.M. and Shaw, J.F. Chronic fluoride intoxication with fluorotic radiculomyelopathy. Ann. Intern. Med., 63(6): 1074–1078 (1965).

103. Goldman, S.M., Sievers, M.L. and Templin, D.W. Radiculomyopathy in a southwestern Indian due to skeletal fluorosis. Ariz. Med., 28(9): 675–677 (1971).

104. Fisher, R.L., Medcalf, T.W. and Henderson, M.C. Endemic fluorosis with spinal cord compression: a case report and review. Arch. Intern. Med., 149(3): 697–700 (1989).

105. Fisher, J.R., Sievers, M.L., Takeshita, R.T. and Caldwell, H. Skeletal fluorosis from eating soil. Ariz. Med., 38(11): 833–835 (1981).

106. Bruns, B.R. and Tytle, T. Skeletal fluorosis. A report of two cases. Orthopedics, 11(7): 1083–1087 (1988).

107. Power, G.R.I. and Gay, J.D.L. Sodium fluoride in the treatment of osteoporosis. Clin. Invest. Med., 9: 41–43 (1986), cited in reference 35.

108. Kleerekoper, M. and Balena, R. Fluorides and osteoporosis. Annu. Rev. Nutr., 11: 309–324 (1991), cited in reference 39.

109. International Agency for Research on Cancer (IARC). Some aromatic amines, anthroquinones and nitroso compounds, and inorganic fluorides used in drinking-water and dental preparations. IARC Monogr. Eval. Carcinog. Risks Chem. Hum., 27 (1982).

110. Keller, C. Fluorides in drinking water. Paper presented at the Workshop on Drinking Water Fluoride Influence on Hip Fracture and Bone Health, Bethesda, MD, April 10 (1991), cited in reference 175.

111. May, D.S. and Wilson, M.G. Hip fractures in relation to water fluoridation: an ecologic analysis. Paper presented at the Workshop on Drinking Water Fluoride Influence on Hip Fracture and Bone Health, Bethesda, MD, April 10 (1991), cited in reference 175.

112. Jacobsen, S.J., Goldberg, J., Cooper, C. and Lockwood, S.A. The association between water fluoridation and hip fracture among white women and men aged 65 years and older. A national ecologic study. Ann. Epidemiol., 2: 617–626 (1992), cited in reference 39.

113. Jacobsen, S.J., O'Fallon, M. and Melton, L.J. Hip fracture incidence before and after fluoridation of the public water supply, Rochester, Minnesota. Am. J. Public Health, 83: 743–745 (1993), cited in reference 39.

114. Danielson, C., Lyon, J.L., Egger, M. and Goodenough, G.K. Hip fracture and fluoridation in Utah's elderly population. J. Am. Med. Assoc., 268: 746–748 (1992), cited in reference 175.

115. Suarez-Almazor, M., Flowerdew, G., Saunders, D., Soskoline, C.L. and Russel, A.S. The fluoridation of drinking water and hip fracture hospitalization rates in two Canadian communities. Am. J. Public Health, 83: 689–693 (1993).

116. Sowers, M., Clark, M.K., Jannausch, M.L. and Wallace, R.B. A prospective study of bone mineral content and fracture in communities with differential fluoride content. Am. J. Epidemiol., 133: 649–660 (1991), cited in reference 39.

117. Cauley, J.A., Murphy, P.A., Riley, T. and Black, D. Public health bonus of water fluoridation: does fluoridation prevent osteoporosis and its related fractures. Am. J. Epidemiol., 134: 768 (1991), cited in reference 175.

118. Inkovaara, J.A. Is fluoride treatment justified today? Calcif. Tissue Int., 49 (Suppl.): S68–S69 (1991), cited in reference 39.

119. Mamelle, N., Dusan, R., Martin, J.L., Prost, A., Meunier, P.J., Guillame, M., Guacher, A. and Zeigler, G. Risk–benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. Lancet (August 13): 361–365 (1988), cited in reference 39.

120. Hedlund, L.R. and Gallagher, J.C. Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. J. Bone Min. Res., 4: 223–225 (1989), cited in reference 39.

121. Riggs, B.L., Hodgson, S.F., O'Fallon, W.M., Chao, E.Y.S., Wahner, H.W., Muhs, J.M., Cedel, S.L. and Melton, L.J. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N. Engl. J. Med., 322: 802–809 (1990), cited in reference 39.

122. Messer, H.H., Armstrong, W.D. and Singer, L. Influence of fluoride intake on reproduction in mice. J. Nutr., 103: 1319–1326 (1973), cited in reference 39.

123. Tao, S. and Suttie, J.W. Evidence for lack of an effect of dietary fluoride level on reproduction in mice. J. Nutr., 106: 1115–1122 (1976), cited in reference 39.

124. Pillai, K.S., Mathai, A.T. and Deshmuhk, P.B. Effect of fluoride on reproduction in mice. Fluoride, 22: 165–168 (1989), cited in reference 39.

125. Chinoy, N.J., Sequeira, E. and Narayanam, M.V. Effect of vitamin C and calcium on the reversibility of fluoride-induced alterations in spermatozoa of rabbits. Fluoride, 24: 29–39 (1991), cited in reference 39.

126. Chinoy, N.J. and Sequeira, E. Reversible fluoride induced fertility impairment in male mice. Fluoride, 25(2): 71–76 (1992).

127. Aulerich, R.J., Napolitano, A.C., Bursian, S.J., Olson, B.A. and Hochstein, J.R. Chronic toxicity of dietary fluoride. J. Anim. Sci., 65: 1759–1767 (1987), cited in reference 39.

128. Susheela, S.K. and Kumar, A. A study of the effect of high concentrations of fluoride on the reproductive organs of male rabbits, using light and scanning electron microscopy. J. Reprod. Fertil., 92: 353–360 (1991), cited in reference 39.

129. Chinoy, N.J. and Sequeira, E. Effects of fluoride on the histoarchitecture of the reproductive organs of the male mouse. Reprod. Toxicol., 3: 261–267 (1989), cited in reference 39.

130. Chinoy, N.J. and Sequeira, E. Fluoride induced biochemical changes in reproductive organs of male mice. Fluoride, 22: 79–85 (1989), cited in reference 39.

131. Kour, K. and Singh, J. Histological finding of mice testes following fluoride ingestion. Fluoride, 13: 160–162 (1980), cited in reference 39.

132. Aschengrau, A., Zierler, S. and Cohen, A. Quality of community drinking water and the occurrence of spontaneous abortion. Arch. Environ. Health, 44: 283–290 (1989), cited in reference 39.

133. Zierler, S., Theodore, M., Cohen, A. and Rothman, K.J. Chemical quality of maternal drinking water and congenital heart disease. Int. J. Epidemiol., 17: 589–594 (1988), cited in reference 39.

134. Aschengrau, A., Zierler, S. and Cohen, A. Quality of community drinking water and the occurrence of late adverse pregnancy outcomes. Arch. Environ. Health, 48: 105–113 (1993), cited in reference 39.

135. Freni, S.C. Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. J. Toxicol. Environ. Health, 42: 109–121 (1994).

136. Glenn, F.B., Glenn, W.D. and Duncan, R.C. Fluoride tablet supplementation during pregnancy for caries immunity: a study of the offspring produced. Am. J. Obstet. Gynecol., 143: 560–564 (1982), cited in reference 39.

137. Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. and Shirasu, Y. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res., 116: 185–216 (1983), cited in reference 39.

138. Tong, C.C., McQueen, C.A., Ved Brat, S. and Williams, G.M. The lack of genotoxicity of sodium fluoride in a battery of cellular tests. Cell Biol. Toxicol., 4: 173–186 (1988), cited in reference 39.

139. Li, Y., Dunipace, A.J. and Stookey, G.K. Absence of mutagenic or antimutagenic activities of fluoride in Ames *Salmonella* assays. Mutat. Res., 190: 229–236 (1987), cited in reference 39.

140. Gocke, E., King, M.-T., Echardt, K. and Wild, D. Mutagenicity of cosmetic ingredients licensed by the European Communities. Mutat. Res., 90: 91–109 (1981), cited in reference 39.

141. Martin, G.R., Brown, K.S., Matheson, D.W., Lebowitz, H.L., Singer, L. and Ophaug, R. Lack of cytogenetic effects in mice or mutations in *Salmonella* receiving sodium fluoride. Mutat. Res., 66(2): 159–167 (1979), cited in reference 39.

142. Litton Bionetics, Inc. Mutagenic evaluation of compound FDA 75-7, 007681-49-4, sodium fluoride. Report prepared for the U.S. Food and Drug Administration (Contract 223-74-2104) by Litton Bionetics, Inc., Kensington, MD (1975), cited in reference 8.

143. Tsutsui, T., Suzuki, N. and Ohmori, M. Sodium fluoride-induced morphological and neoplastic transformation, chromosome aberrations, sister chromatid exchanges and unscheduled DNA synthesis in cultured Syrian hamster embryo cells. Cancer Res., 44: 938–941 (1984), cited in reference 39.

144. Jones, C.A., Callahan, M.F. and Huberman, E. Sodium fluoride promotes morphological transformation of Syrian hamster embryo cells. Carcinogenesis, 9: 2279–2284 (1988), cited in reference 39.

145. Jones, C.A., Huberman, E., Callahan, M.F., Tu, A., Halloween, W., Pallota, S., Sivak, A. Lubet, R.A., Avery, M.D., Kouri, R.E., Spalding, J. and Tennant, R.W. An inter-laboratory evaluation of the Syrian hamster embryo cell transformation assay using fourteen coded chemicals. Toxicol. In Vitro, 2: 103–116 (1988), cited in reference 39.

146. Lasne, C., Lu, Y.-P. and Chouroulinkov, I. Transforming activities of sodium fluoride in cultured Syrian hamster embryo and BALB/3T3 cells. Cell Biol. Toxicol., 4: 311–324 (1988), cited in reference 39.

147. Cole, J., Muriel, W.J. and Bridges, B.A. The mutagenicity of sodium fluoride to L5178Y [wild-type and TK+/– (3.7.2C)] mouse lymphoma cells. Mutagenesis, 1: 157–167 (1986), cited in reference 39.

148. Caspary, W.J., Myhr, B., Bowers, L., McGregor, D., Riach, C. and Brown, A. Mutagenic activity of fluorides in mouse lymphoma cells. Mutat. Res., 187: 165–180 (1987), cited in reference 39.

149. Caspary, W.J., Langenbach, R., Penman, B.W., Crespi, C., Myhr, B. and Mitchell, A.D. The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells. Mutat. Res., 196: 61–81 (1988), cited in reference 39.

150. Crespi, C.L., Seixas, G.M., Turner, T. and Penman, B.W. Sodium fluoride is a less efficient human cell mutagen at low concentrations. Environ. Mol. Mutagen., 15: 71–77 (1990), cited in reference 39.

151. Moore, M.M., Clive, D., Hozier, J.C., Howard, B.E., Batsun, A.G., Turner, N.N. and Sawyer, J. Analysis of trifluorothymidine resistant (TFT') mutants of L5178Y/TK$^{\pm}$ mouse lymphoma cells. Mutat. Res., 151: 161–174 (1985), cited in reference 39.

152. Tsutsui, T., Suzuki, N., Ohmori, M. and Maizumi, H. Cytotoxicity, chromosome aberrations and unscheduled DNA synthesis in cultured human diploid fibroblasts induced by sodium fluoride. Mutat. Res., 139: 193–198 (1984), cited in reference 39.

153. Tsutsui, T., Koichi, I. and Maizumi, H. Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. Mutat. Res., 140: 43–48 (1984), cited in reference 39.

154. Skare, J.A., Wong, T., Evans, L.B. and Cody, D.B. DNA-repair studies with sodium fluoride: comparative evaluation using density gradient ultracentrifugation and autoradiography. Mutat. Res., 172: 77–87 (1986), cited in reference 39.

155. Tong, C., McQueen, C.A., VedBrat, S. and Williams, G.M. The lack of genotoxicity of sodium fluoride in an *in vitro* test battery. Environ. Mutagen., 8 (Suppl. 6): 86 (abstr.) (1986), cited in reference 39.

156. Scott, D. Cytogenetic effects of sodium fluoride in cultured human fibroblasts. Mutagenesis, 1: 69 (abstr.) (1986), cited in reference 39.

157. Scott, D. and Roberts, S.A. Extrapolation from *in vitro* tests to human risk: experience with sodium fluoride clastogenicity. Mutat. Res., 189: 47–58 (1987), cited in reference 39.

158. Aardema, M.J., Gibson, D.P. and LeBoeuf, R.A. Sodium fluoride induced chromosome aberrations in different stages of the cell cycle: a proposed mechanism. Mutat. Res., 223: 191–203 (1989), cited in reference 39.

159. Kishi, K. and Tonomura, A. Cytogenic effects of sodium fluoride. Mutat. Res., 130: 367 (abstr.) (1984), cited in reference 39.

160. Thomson, E.J., Kilanowski, F.M. and Perry, P.E. The effect of fluoride on chromosome aberration and sister chromatid exchange frequencies in cultured human lymphocytes. Mutat. Res., 144: 89–92 (1985), cited in reference 39.

161. Li, Y., Heerema, N.A., Dunipace, A.J. and Stokey, G.K. Genotoxic effects of fluoride evaluated by sister-chromatid exchange. Mutat. Res., 192: 191–201 (1987), cited in reference 39.

162. Li, J., Suzuki, Y., Hayashi, K. and Shimizu, H. The genotoxic effect of sodium fluoride. Mutat. Res., 252: 95 (abstr.) (1991), cited in reference 39.

163. Dominok, B. and Miller, G.W. Effects of fluoride on *Drosophila melanogaster* in relation to survival and mutagenicity. Fluoride, 23: 83–91 (1990), cited in reference 39.

164. Mitchell, B. and Gerdes, R.A. Mutagenic effects of sodium and stannous fluoride on *Drosophila melanogaster*. Fluoride, 6: 113–117 (1973), cited in reference 39.

165. Kram, D., Schneider, E.I., Singer, L. and Martin, G.R. The effects of high and low fluoride diets on the frequencies of sister chromatid exchanges. Mutat. Res., 57: 51–55 (1978), cited in reference 39.

166. Li, Y., Zhang, W., Noblitt, T.W., Dunipace, A.J. and Stookey, G.K. Genotoxic evaluation of chronic fluoride exposure: sister-chromatid exchange study. Mutat. Res., 227: 159–165 (1989), cited in reference 39.

167. Zeiger, E., Shelby, M.D. and Witt, K.L. Genetic toxicity of fluoride. Environ. Mol. Mutagen., 21: 309–318 (1993), cited in reference 39.

168. Li, Y., Dunipace, A.J. and Stookey, G.K. Lack of genotoxic effects of fluoride in the mouse bone-marrow micronucleus test. J. Dent. Res., 66: 1687–1690 (1987), cited in reference 39.

169. Dunipace, A.J., Zhang, W., Noblitt, T.W., Li, Y. and Stookey, G.K. Genotoxic evaluation of chronic fluoride exposure: micronucleus and sperm morphology studies. J. Dent. Res., 68: 1525–1528 (1989), cited in reference 39.

170. Albanese, R. Sodium fluoride and chromosome damage (*in vitro* human lymphocytes and *in vivo* micronucleus assays). Mutagenesis, 2: 497–499 (1987), cited in reference 39.

171. Li, Y., Dunipace, A.J. and Stookey, G.K. Effects of fluoride on the mouse sperm morphology test. J. Dent. Res., 66: 1509–1511 (1987), cited in reference 39.

172. Pati, P.C. and Bhunya, S.P. Genotoxic effect of an environmental pollutant, sodium fluoride in mammalian *in vivo* test system. Caryologia, 40: 79–87 (1987), cited in reference 39.

173. Ma, J., Cheng, L., Bai, W. and Wu, H. The effects of sodium fluoride on SCEs of mice and on micronucleus of the bone marrow of pregnant mice and fetal liver. Yichuan/Hereditas, 8: 39–41 (1986), cited in reference 39.

174. Hayashi, M., Kishi, M. and Ishidate, M. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem. Toxicol., 26: 487–500 (1988), cited in reference 39.

175. U.S. National Research Council. Health effects of ingested fluoride. Report of the Subcommittee on Health Effects of Ingested Fluoride. National Academy Press, Washington, DC (1993).

176. Freni, S.C. and Gaylor, D.W. International trends in the incidence of bone cancer are not related to drinking water fluoridation. Cancer, 70: 611–618 (1992), cited in reference 39.

177. Hoover, R.N., De Vesa, S.S., Cantor, K.P., Lubin, J.H. and Fraumeni, J.F., Jr. Fluoridation of drinking water and subsequent cancer incidence and mortality. Appendix E in: Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Review of fluoride benefits and risks. Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC, February (1991), cited in reference 39.

178. Hoover, R.N., De Vesa, S.S., Cantor, K.P. and Fraumeni, J.F., Jr. Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program, National Cancer Institute. Appendix F in: Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Review of fluoride benefits and risks. Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC, February (1991), cited in reference 39.

179. Knox, E.G. Fluoridation of water and cancer: a review of the epidemiological evidence. Report of the British Working Party. Her Majesty's Stationery Office, London, UK (1985).

180. U.S. National Research Council. Drinking water and health. Report of the Safe Drinking Water Committee. National Academy Press, Washington, DC. pp. 381–389 (1977), cited in reference 8.

181. Burt, B.A. The changing patterns of systemic fluoride intake. J. Dent. Res., 71 (Spec. Iss.): 1228–1237 (1992).

182. Fejerskov, O., Manji, F. and Baelum, V. The nature and mechanisms of dental fluorosis in man. J. Dent. Res., 69 (Spec. Iss.): 692–700 (1990).

183. Cutress, T.W. and Suckling, G.W. Differential diagnosis of dental fluorosis. J. Dent. Res., 69 (Spec. Iss.): 714–721 (1990).

184. Smith, G.E. Fluoride and fluoridation. Soc. Sci. Med., 26(4): 451–462 (1988).

185. Clark, D.C. Trends in prevalence of dental fluorosis in North America. Commun. Dent. Oral Epidemiol., 22(3): 148–152 (1994).

186. Limeback, H. Enamel formation and the effects of fluoride. Commun. Dent. Oral Epidemiol., 22(3): 144–147 (1994).

187. Evans, R.W. and Stamm, J.W. An epidemiologic estimate of the critical period during which maxillary central incisors are most susceptible to fluorosis. J. Public Health Dent., 51(4): 251–259 (1991).

188. Advisory Review Panel. Recommendations regarding fluoride intake. Investigation of inorganic fluoride and its effects on the occurrence of dental caries and dental fluorosis in Canada. Report prepared for the Department of National Health and Welfare under Research Contract No. 3726 (1993).

189. Dean, H.T., Arnold, F.A., Jr. and Elvove, E. Domestic water supplies and dental caries. V. Additional studies of the relation of fluoride domestic waters to caries experience of 4,425 white children, aged 12–14 years, of 13 cities and 4 states. Public Health Rep., 57: 1155–1179 (1942).

190. Dean, H.T., Jay, P., Arnold, F.A., Jr. and Elvove, E. Domestic water and dental caries. II. A study of 2,832 white children aged 12–14 years of 8 suburban Chicago communities. Including *Lactobacillus acidophilus* studies of 1,761 children. Public Health Rep., 56: 761–792 (1941).

191. Clark, D.C. Working group report on the ingestion of inorganic fluoride and its effect on the occurrence of dental caries and dental fluorosis in Canada. In: Investigation of inorganic fluoride and its effects on the occurrence of dental caries and dental fluorosis in Canada. Report prepared for the Department of National Health and Welfare under Research Contract No. 3726 (1993).

192. Ismail, A.I. Dental caries, fluorosis, and fluorides. In: Investigation of inorganic fluoride and its effects on the occurrence of dental caries and dental fluorosis in Canada. Report prepared for the Department of National Health and Welfare under Research Contract No. 3726 (1993).

193. Eklund, S.A. and Striffler, D.F. Anticaries effect of various concentrations of fluoride in drinking water: Evaluation of empirical evidence. Public Health Rep., 95: 486–490 (1980).

194. McClure, F.J. Ingestion of fluoride and dental caries. Quantitative relations based on food and water requirements of children one to twelve years old. Am. J. Dis. Child., 66: 362–369 (1943).

195. Thylstrup, A. Clinical evidence of the role of pre-eruptive fluoride in caries prevention. J. Dent. Res., 69 (Spec. Iss.): 742–750 (1990).

196. Beltran, E.D. and Burt, B.A. The pre- and posteruptive effects of fluoride in the caries decline. J. Public Health Dent., 48(4): 233–240 (1988).

197. Groeneveld, A., Van Eck, A.A.M.J. and Backer Dirks, O. Fluoride in caries prevention: is the effect pre- or post-eruptive? J. Dent. Res., 69 (Spec. Iss.): 751–755 (1990).

198. Grembowski, D., Fiset, L. and Spadafora, A. How fluoridation affects adult dental caries. Systemic and topical effects are explored. J. Am. Dent. Assoc., 123: 49–54 (1992).

199. Hunt, R.J., Eldridge, J.B. and Beck, J.D. Effect of residence in a fluoridated community on the incidence of coronal and root caries in an older population. J. Public Health Dent., 49: 138–141 (1989).

200. Riordan, P.J. Perceptions of dental fluorosis. J. Dent. Res., 72(9): 1268–1274 (1993).

201. Riordan, P.J. Specialist clinicians' perceptions of dental fluorosis. J. Dent. Child., 60(4–5): 315–320 (1993).

202. Clark, D.C. Evaluation of aesthetics for the different classifications of the tooth surface index of fluorosis. Commun. Dent. Oral Epidemiol., 23: 80–83 (1995).

203. Health Canada. Guidelines for Canadian drinking water quality. 6th edition. Prepared by the Federal–Provincial Subcommittee on Drinking Water of the Federal–Provincial Committee on Environmental and Occupational Health. Canada Communication Group — Publishing, Ottawa (1996).

204. Department of National Health and Welfare. Guidelines for Canadian drinking water quality 1978. Supporting documentation. Supply and Services Canada, Ottawa (1980).