

Finding #2 – The Risk of Drinking Water Fluoridation

In this section, the Fluoride Technical Study Group (FTSG) summarizes the evidence from toxicologic and epidemiologic studies that addresses the potential for community water fluoridation to cause adverse health outcomes in the community. The major outcomes considered include cancer, effects on bone, dental enamel fluorosis, effects on the immune system and effects on thyroid function. While the focus of this evaluation is on potential risks from the city's practice of drinking water fluoridation at 1mg/l, the risks from total fluoride dose including other sources is also considered.

Total Exposure to Fluoride

The FTSG evaluated total consumption of fluoride from all sources so that the likelihood of health risks from fluoridation could be evaluated for the appropriate potential total dose, not just the dose from water fluoridation. The sources of fluoride intake for the U.S. population are primarily water, food, and dental products (Tables 4 and 5). Although fluoride exposure is generally greater in areas with fluoridated water than in areas with nonfluoridated or low-fluoridated water, populations in both areas are exposed to fluoride from food sources, drinking water, processed beverages and dental products. According to the US Public Health Service:

"In optimally fluoridated areas, most of the estimated daily intake of fluoride for children and adults is from drinking water, beverages and food. In low-fluoride or non-fluoridated areas, children can receive their highest proportion of daily intake from fluoride supplements and dentifrice[see Table 3]. The daily intake of most adults is about equally divided among food, drinking water, beverages, and mouthrinses [see Table 4 below]." (Committee to Coordinate Environmental Health and Related Programs, USPHS [USPHS], 1991, p. 15).

Dietary sources of fluoride (other than drinking water) are outlined in Table 1.

Table 1

Fluoride Concentrations (mg/L or Kg) in Food (adapted from USPHS, Table 5, p.11)

Foods (Note A)	Mean (mg/L or Kg)	Standard Deviation	Range
Dairy Products	0.25	0.38	0.02 - 0.82
Meat Fish & Poultry	0.22	0.15	0.04 - 0.51
Grain & Cereal Products	0.42	0.40	0.08 - 2.01
Potatoes	0.49	0.26	0.21 - 0.84
Leafy Vegetables	0.27	0.25	0.21 - 0.84
Legumes	0.53	0.05	0.49 - 0.57
Root Vegetables	0.38	0.11	0.27 - 0.48
Fruits	0.06	0.03	0.02 - 0.08
Oils & Fats	0.25	0.15	0.02 - 0.44
Sugar and Adjuncts	0.28	0.27	0.02 - 0.78
Nonclassifiable Foods	0.59	0.19	0.29 - 0.87

Note: The foods were ready to eat or prepared for eating. When preparation required the use of water (e.g. preparing juice from concentrate or boiling vegetables), the local water was used which contained 1 mg/L (1 ppm) of fluoride. Nonclassifiable foods included certain soups and puddings, among other items.

Most foods have fluoride concentrations below 0.5 mg/liter or kg (Dabeka & McKenzie, 1995). Among beverages the highest amounts of fluoride are reported in teas. Due to the ability of tea leaves to

concentrate fluoride, brewed tea contains fluoride ranging from 1 to 6 mg/liter depending on amount, brewing time and fluoride concentration in water (USPHS, 2000, p. 294).

Intake from fluoridated dental products sometimes exceeds that from diet, particularly in young children who swallow toothpaste due to poor control of the swallowing reflex. An average of about 0.3 mg of fluoride is introduced with each brushing in young children (USPHS, 2000, p. 296). In communities with low levels of fluoride in the water supply, oral fluoride supplements are recommended by the American Academy of Pediatrics, American Dental Association, and the American Academy of Family Physicians. Table 2 shows the 1995 recommended supplement endorsed by these associations. No supplement is recommended for children under six months of age.

Table 2

Recommended Fluoride Supplementation (mg/day) for Children of Different Ages at Different Drinking Water Fluoride Concentrations

Drinking Water Fluoride Concentration	Fluoride Supplements			
	Child Age 0 to 6 Months	Child Age 6 to 36 Months	Child Age 3 to 6 Years	Child Age 6 to 10 Years
<0.3 ppm	Not recommended	0.25 mg/day	0.5 mg/day	1.0 mg/day
0.3-0.6 ppm	Not recommended	Not recommended	0.25 mg/day	0.5 mg/day
>0.6 ppm	Not recommended	Not recommended	Not recommended	Not recommended

Reference

(1) American Academy of Pediatrics, (1995) Committee on Nutrition, *Pediatrics*, 95, 777; also endorsed by the American Dental Association and the American Academy of Family Physicians.

According to the Institute of Medicine:

“Based on the 1986 National Health Interview Survey (NHIS) data, it is estimated that 15 percent of children in the United States up to age 5 years and 8 percent of children 5 to 17 years old use dietary fluoride supplements. Fluoride supplements are rarely prescribed for adults” (Committee on the Scientific Evaluation of Dietary Reference Intakes, Institute of Medicine [IOM], 2000, p. 295).

Tables 3 and 4 illustrate the ranges of fluoride intake (mg/day) for children and adults from all sources in areas with water fluoridated at three different levels, including 1 mg/L fluoride. The ranges presented are estimated total intakes extrapolated from published studies and are not derived from data measured in individuals. The maximum values are derived by summing the highest intakes reported in published literature for each type of ingested fluoride source. The estimates also assume that adults in both optimally fluoridated and non-fluoridated areas use fluoride mouth-rinse twice daily.

Table 3

Estimated Daily Fluoride Intake of Child Weighing 20kg (44 lbs)^a (adapted from USPHS, 1991, Table 10, p. 16)

Fluoride in Water (mg/L)	Intake from Food ^b in mg/day (mg/kg/day)	FI Containing Beverages ^b in mg/day (mg/kg/day)	Fluoride Dentifrices ^c in mg/day (mg/kg/day)	F Supplements ^d in mg/day (mg/kg/day)	Estimated Total Intake in mg/day (mg/kg/day)
<0.3	0.15-0.3 (0.007-0.015)	0.1-0.3 (0.005-0.015)	0.2-1.2 (0.01-0.06)	0.50 (0.025)	0.95-2.3 (0.047-0.115)
0.7-1.2	0.4-0.6 [0.02-0.03]	0.3-1.8 [0.015-0.09]	0.2-1.2 [0.01-0.06]	Not recommended	0.9-3.6 [0.045-0.18]
>2.0	1.0-2.0 [0.05-0.10]	0.6->3.0 [0.03-0.15]	0.2-1.2 [0.01-0.06]	Not recommended	1.8->6.2 [0.09-0.31]

a Calculations based on child weighing 20 kg (44 lbs)

b Based on ranges of data extrapolated from various literature sources by PHS.

c Assumed that dentifrice used twice daily

d Assumed that dental fluoride supplement taken daily

Table 4

Estimated Daily Fluoride Intake of Adult Weighing 50 kg (110 lbs)^a
(adapted from USPHS, Table 11, p. 17)

Fluoride in Water (mg/L)	Intake from Food ^b in mg/day (mg/kg/day)	FI Containing Beverages ^b in mg/day (mg/kg/day)	Fluoride Dentifrices ^c in mg/kg (mg/kg/day)	F Mouthrinse ^c in mg/kg (mg/kg/day)	Estimated Total Intake in mg/kg (mg/kg/day)
<0.3	0.2-0.8 (0.004-0.016)	0.1-0.7 (0.002-0.014)	0.018-0.145 (0.0004-0.003)	0.56 (.010)	0.88-2.20 (0.016-0.40)
0.7-1.2	0.4-2.7 [0.008-0.54]	0.6-3.2 [0.012-0.064]	0.018-0.145 [0.0004-0.003]	0.56 [0.01]	.58-6.6 [0.03-0.13]
>2.0	1.2-3.4 [0.02-0.07]	0.9->3.5 [0.018->0.07]	0.018-0.145 [0.0004-0.003]	Not recommended	2.1->7.05 [0.04->0.14]

a Calculations based on adult weighing 50 kg (110 lbs)

b Based on ranges of data extrapolated from various literature sources by PHS.

c Assumed that dentifrice and mouth-rinse are used twice daily

According to the Institute of Medicine:

“Ten independent U.S. and Canadian studies published from 1958 to 1987 have shown that dietary fluoride intakes by adults range from 1.4 to 3.4 mg/day in areas where the water fluoride concentration was 1.0 mg/liter. In areas where the water fluoride concentration was less than 0.3 mg/liter, the daily intakes ranged from 0.3 to 1.0 mg/liter day” (IOM, 2000, p. 293).

Table 5 shows the *average* total daily intake of fluoride by age.

Table 5
Average Intake of Dietary Fluoride by Age

(Whitford, 1994, p. 6)

Age	Mg F/Day	Mg F/Kg/Day	Reference
0-6 months			
Breast-fed	<0.01	<0.003	Ekstrand et al., 1984
Formula-fed:			
Ready-to-feed	<0.4	<0.13	Johnson and Bawden, 1987
Reconstituted ^a	ca. 1.0	<0.30	McKnight-Hanes et al., 1988
6 months	0.2-0.5 ^b	0.03-0.07	Ophaug et al., 1980a
2 years	0.3-0.6 ^b	0.02-0.05	Ophaug et al., 1980b
Adult	1.2	0.016-0.022 ^c	Singer et al., 1980
	1.8	0.023-0.033 ^c	Taves, 1983
	2.2	0.029-0.040 ^c	SanFilippo & Battsonte, 1971

a Reconstituted with water fluoridated at 1 ppm.

b Lower value is for nonfluoridated water. Higher value is for optimally fluoridated water.

c Range calculated for persons with body weights of 75 kg and 55 kg whose drinking water is optimally fluoridated.

Dietary reference intakes established by the Institute of Medicine (IOM, 2000) include adequate intake levels set for all children and adults at 0.05 mg/kg/day. For infants newborn to six-months old the recommended amount (based on the amount found in breast milk) is 0.01 mg/day. The upper limit set to protect against moderate dental fluorosis is 0.1 mg/kg/day for all ages. This upper limit of 0.7 mg/day, assuming a seven kg infant weight, can be exceeded in optimally fluoridated water communities when water of 1.0 mg/l of fluoride is used to make reconstituted formula and fed to infants less than six months old. The upper limit set for infants 7 to 12 months is 0.9 mg/day. The Institute of Medicine set the upper limits for children age 1 to 3 at 1.3 mg/day and age four to eight at 2.2 mg/day based on reference weights of 13 kg and 22 kg respectively.

The FTSG noted that for children six months to six years, total fluoride consumption from food and beverages nearly equals the recommended adequate intake levels of 0.05 mg/kg/day. If excess water or beverages are consumed or fluoridated toothpaste is inappropriately eaten, fluoride levels may exceed the 0.1 mg/kg/day upper limit standard and may cause dental fluorosis. Repeated over-ingestion during the formative years of tooth development (three months to six years) may result in varying degrees of dental fluorosis on a dose-dependent scale. After age six to seven, all anterior (front) teeth have completed their enamel formation, and after age eight, all but the wisdom teeth crowns are formed. The risk of moderate dental fluorosis is low because of the low likelihood of exposures at the extremes of the range presented in Table 3. The estimated upper range of the total intakes in Table 3 exceeds the values set by the Institute of Medicine to be protective of moderate dental fluorosis. The upper limit established for children older than 8 years and adults is 10 mg/day. This level is not exceeded at optimal levels of water fluoridation.

Several regulatory bodies have determined thresholds for safe daily intake of fluoride based on potential adverse effects (tooth or bone effects). The Agency for Toxic Substances and Disease Registry (ATSDR) has set a chronic Minimal Risk Level (MRL) for ingestion of fluoride at 0.05 mg/kg/day (ATSDR: <http://www.atsdr.cdc.gov/mrls.html>). The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over

a specified duration of exposure. The ATSDR based this on a lowest observed adverse event level for increased fracture rates (see “Bone Effects” section below), and divided it by a “safety factor” of 10. The U.S. EPA has established a “reference dose,” a standard similar to the MRL, of 0.06mg/kg/day, based on a “no-observed adverse effect level” for mottling of the teeth (see “Enamel Fluorosis” section below). The FTSG noted that there is a narrow “margin of safety” when comparing average daily intake of fluoride in Table 5 with these levels.

Fluoride Exposure Uncertainties

The gaps in knowledge regarding total fluoride exposure from all sources are captured in the following summaries:

In the “Tier One” literature, the Medical Research Council of Great Britain noted several uncertainties with regard to total fluoride exposure estimates and the impacts of total exposure uncertainties on health effects assessments cited as follows:

“As previously recounted, developments since 1960 have altered the general pattern of fluoride exposure and may have created a new situation in the population at large, both with respect to total exposure and the main sources of exposure. There are therefore several deficiencies in the existing body of evidence when evaluating effects relating to fluoride exposure, and other questions that need to be addressed: The effects of fluorides are probably related to total exposure, not just fluoride in drinking water. There are very few data relating total fluoride exposure to health effects” (Medical Research Council [MRC], 2002, p. 14).

In general, the absorption of fluoride ion into the body (called “bioavailability”) is high, however it depends to a certain extent on the nature of the vehicle it is ingested with. According to the Institute of Medicine’s Dietary Reference Intake Guide, “If it is ingested with milk, baby formula, or foods, especially those with high concentrations of calcium or certain other divalent or trivalent ions that form insoluble compounds, absorption may be reduced by 10-25%” (IOM, 2000, p.291).

The Medical Research Council of Great Britain recommends the following:

“New studies are required to investigate the bioavailability and absorption of fluoride from naturally fluoridated and artificially fluoridated drinking water, looking also at the impact of water hardness. This is particularly important because if the bioavailability is the same, many of the findings relating to natural fluoride can also be related to artificial fluoridation.

Further attempts should be made to calculate lifetime intakes of fluoride, using both urinary and ingestion data, and to determine the relative contribution of fluoride in artificially fluoridated water to total fluoride uptake. If the bioavailability of artificial and natural fluoride are found to be the same, then studies on people who have lived in naturally high fluoride areas could be informative” (MRC, 2002, p. 15).

Other observations have appeared in the peer-reviewed literature and in the summaries of review panels.

“Investigators seeking to examine possible relations between fluoride intake and biological effects or health outcomes, such as dental fluorosis or the quality of bone or its strength, need to be aware of the complex situation that exists today. It is no longer feasible to estimate with reasonable accuracy the level of fluoride exposure based simply on the concentration of the ion in the drinking water” (Whitford, 1994, pp. 7-8).

“There was considerable concern amongst many Taskforce members that water fluoridation could increase the total intake of fluoride in excess of a safe level for babies and young children. The evidence relating to what constituted a safe or a toxic dose of fluoride was uncertain and confusing.

A majority of Taskforce members were concerned that the margin of safety between a safe and toxic dose may not be sufficiently wide” (The Lord Mayor's Taskforce on Fluoridation, 1997, p. 89)

FINDINGS: Total Fluoride Exposure

Total fluoride exposure must be considered when evaluating health effects. The amount of total fluoride ingested will vary between individuals and is not precisely known. The FTSG review of the literature finds that likely total exposure values for children older than six months living in communities with water fluoridated at up to 1.2 mg/L (ppm) do not exceed the upper limit set to be protective of moderate dental fluorosis by the Institute of Medicine. Total dietary exposures of fluoride can exceed this threshold amount (0.7mg/day) in infants fed formula reconstituted with optimally fluoridated water.

Review of Potential Adverse Health Effects

Our review of the literature, consistent with community input, indicates that there are four major potential health concerns associated with long-term exposure to fluoride: cancer, bone fractures, skeletal fluorosis and dental enamel fluorosis, and several other conditions for which a much more limited literature database is available. In this section, we present a summary of the evidence on the likelihood of specific health risks from drinking water fluoridation. We also include more comprehensive documentation of the literature reviewed in Appendix 2 to this report.

As described in more detail in the introduction, the FTSG reviewed the toxicological and epidemiological studies for each of these outcomes as independent lines of evidence. The group considered the weight of evidence findings as stronger when the toxicological and epidemiological studies were in agreement. The weight of evidence conclusions are more uncertain when these two independent lines of evidence disagree with regard to the likelihood of health risks from water fluoridation.

Cancer

Animal Toxicological Studies

There have been two major, recent animal studies that explored the possibility that long-term exposure to fluoride causes cancer. These studies have been examined by a number of federal agencies and their interpretations and conclusions of these data are provided below. The first animal toxicology study, conducted by the National Toxicology Program (NTP), administered fluoride at concentrations of up to 175 mg/L of drinking water [approximately 79 times the concentration in Fort Collins water]. “Although the results were negative for male and female mice and female rats, there was some evidence of a dose-related increase in the incidence of osteosarcomas in male rats” (National Research Council [NRC], 1993, p. 10).

The Agency for Toxic Substances and Disease Registry of the U.S. Public Health Service (ATSDR) summarized the NTP study as follows:

“Based on the finding of a rare tumor in a tissue known to accumulate fluoride, but not at the usual site for chemically-associated osteosarcomas, a weakly significant dose-related trend, and the lack of supporting data in female rats and mice of either gender, the NTP concluded that there was ‘equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats.’ NTP defined equivocal evidence of carcinogenic activity to be a situation where the results show ‘a marginal increase in neoplasms that may be chemically related.’ NTP further concluded that there

was no evidence that fluoride was carcinogenic at doses up to 4.73 mg/kg/day¹ in female N344/N rats, or at doses up to 17.8 and 19.9 mg/kg/day in male and female B6C3F₁ mice, respectively” (Agency for Toxic Substances and Disease Registry [ATSDR], 2001, p. 100).

A second study, sponsored by Proctor and Gamble examined carcinogenic potential of sodium fluoride administered in feed to Sprague-Dawley rats and CD-1 mice. The data from the Proctor and Gamble Study were reviewed by the Carcinogenicity Assessment Committee, Center for Drug Evaluation and Research, Food and Drug Administration (CAC/CDER/FDA) who reported that statistical analysis of the incidence of bone tumors found no dose-response relationship and that:

“The CAC review concluded that there were flaws and uncertainties in the studies that keep them from providing strongly reassuring data. However, the committee concluded that the study results reaffirm the negative finding of the NTP study in female rats, and do not reinforce equivocal findings in male rats” (as cited by ATSDR, 2001, p. 101).

However, these results were not confirmed by:

“a ...study conducted by Procter & Gamble, in which fluoride was administered in the diet at doses higher than those in the NTP study. The Procter & Gamble study did produce a significant dose-related increase in the incidence of osteomas (benign bone tumors) in male and female mice. However, these lesions were not considered to be neoplastic and, in any event, have no known counterpart in human pathology” (NRC, 1993, p. 10-11).

Subsequently, the data from both of these toxicology studies were reviewed by the National Research Council and a U.S. Public Health Service committee. The National Research Council subcommittee concluded, “the available laboratory data are insufficient to demonstrate carcinogenic effects of fluoride in animals” (NRC, 1993, p. 11).

Similarly, the U.S. Public Health Service committee concluded:

“When the NTP and the Proctor and Gamble studies are combined, there is a total of eight individual sex/species groups examined. Seven of these groups showed no significant evidence of malignant tumor formation. One of these groups, male rats from the NTP study, showed “equivocal” evidence of carcinogenicity, which is defined by NTP as a marginal increase in neoplasms – i.e. osteosarcomas – that may be chemically related. Taken together, the two animal studies available at this time fail to establish an association between fluoride and cancer” (USPHS, 1991, p. 76).

Human Epidemiological Studies

The potential for an association between human cancer and exposure to fluoridated water has also been explored in many epidemiologic studies and summarized in reviews conducted by the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, the World Health Organization, the National Research Council, National Academy of Science, the U.S. Public Health Service, and the Medical Research Council of Great Britain. Relevant citations from the texts of these reviews follow; a fuller description of each is found in Appendix 2.

¹ As typically practiced in animal toxicology studies these doses are about 100-400 times the average dose in humans in fluoridated communities. The 4.73 mg/kg/day dose is approximately equivalent to an average adult in Fort Collins drinking about 100 gallons of water per day for a lifetime.

The Agency for Toxic Substances and Disease Registry, U.S. Public Health Service (ATSDR) summarized the epidemiological studies of human cancer as follows:

“Numerous epidemiological studies have examined the issue of a connection between fluoridated water and cancer. The weight of evidence indicates that no such connection exists. However, all of the investigations were ecologic studies, and the sensitivity limit of even the most sensitive analysis in these studies appears to be a 10-20% increase in risk” (ATSDR, 2001, p. 96).

A large epidemiological study conducted by the National Cancer Institute was summarized by ATSDR as follows:

“An epidemiological study (Hoover et al. 1991) examined >2,300,000 cancer deaths and 125,000 cancer cases in U.S. counties exposed to artificially fluoridated drinking water for up to 35 years. Taking into account the results of the NTP study... detailed analyses were conducted of cancers of the joints and bones (especially osteosarcomas), and cancers of the oral cavity and pharynx. The statistical evaluation was based on analysis of time trends in the observed/expected (O/E) ratios relative to duration of fluoridation. While elevated O/Es were observed for osteosarcomas in males, the O/E ratio was inversely related to duration of fluoridation. Thorough analyses of incidences of oral cancers and cancers at a variety of other sites were conducted by means of very sensitive statistical tests that were designed to detect changes as small as 10-20%. No consistent correlation between cancer incidence or mortality and duration of fluoridation was found. An addendum to the report noted that the age-adjusted national incidence of osteosarcomas increased by 18% in males for the years 1973-80 and 1981-87; most of the increase was due to a 53% increase in males under 20 years of age, and there was a larger increase in fluoridated than nonfluoridated areas. A similar time-trend analysis to that done in the main report found no correlation between the cancer incidence O/E ratio and duration of fluoridation. Additional analyses also failed to find a relationship between osteosarcoma incidence in males and exposure to water fluoridation” (ATSDR, 2001, p. 98).

The National Research Council (National Academy of Sciences) examined the epidemiologic studies of cancer and exposure to fluoridated drinking water and came to the following conclusion:

“More than 50 epidemiological studies have examined the relation between fluoride concentrations in drinking water and human cancer. Most studies compared geographic or temporal patterns of cancer occurrences with distributions of fluoride in drinking water. These studies provide no credible evidence for an association between fluoride in drinking water and the risk of cancer” (NRC, 1993, p. 10).

The National Research Council Committee concluded that “the weight of the evidence from the epidemiological studies completed to date does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans” (NRC, 1993, p. 11).

A committee appointed by the U.S. Public Health Service to review the risks and benefits of fluoride summarized their findings regarding potential cancer risk as follows:

“The ad hoc subcommittee of the Committee to Coordinate Environmental Health and Related Programs reviewed the results from numerous epidemiologic studies of the relation between exposure to fluoridated water and cancer that have been conducted during the last 40 years. In addition to the review of these studies, the Subcommittee reviewed the findings of a recent study from the National Cancer Institute (NCI), which updated and expanded an earlier county-specific analysis for cancer mortality in the United States in relation to water fluoridation.... Both this report and reports from previous international expert panels which have reviewed earlier data concluded that there is no credible evidence of any association between the risk of cancer and

exposure to either natural or adjusted fluoride in drinking water” (USPHS, 1991, Executive Summary, p. 4).

Several international bodies have also examined the potential for cancer risk from consumption of fluoridated water. The NHS Center at the University of York in Great Britain review (2000) included 26 studies of the association of water fluoridation and cancer, 21 of these studies were from the lowest level of evidence, level C, with the highest risk of bias, and five from level B. Among the 10 studies that examined the relationship between fluoride exposure and all-cause cancer incidence and mortality, only two studies found a statistically significant association: one found a mixed effect with more cancer in two of eight subgroups, while the other found a significant protective effect (fewer cancers) in persons exposed to drinking water fluoride. The possible relationship between fluoride exposure and cancers of bone is of particular interest because fluoride accumulates in bone. Contained in the four studies meeting the inclusion criteria established by the NHS in which the association between water fluoride exposure and bone related cancer was examined, there were eight analyses. Four analyses found the direction of association to be positive (fewer bone cancers in those exposed to fluoride) and three found the direction to be negative (more cancers in those exposed to fluoride). Similarly, among the 12 analyses of the association between water fluoride exposure and osteosarcoma (a rare tumor derived from bone producing cells called osteoblasts), seven found fewer tumor cases; three found more tumor cases and two found no association. Only one study found a statistically significant association between fluoridation and either bone related cancer or osteosarcoma. This study found an increased prevalence of osteosarcoma in males but not females. This study however, also had the lowest validity score (NHS Centre for Reviews and Dissemination, University of York [NHS], 2000, pp. 54-57). The NHS reviewers concluded:

“There is no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers. Only two studies considered thyroid cancer and neither found a statistically significant association with water fluoridation. Overall, no clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer or all cancers was found” (NHS, 2000, p. xiii).

In the most recent of these reviews, the Medical Research Council of Great Britain examined an earlier analysis by the University of York (the NHS review discussed above) as well as earlier studies and reviews. The Medical Research Council concluded:

“The evidence available does not suggest that fluoridation of water increases the risk for cancer in general or for any particular type of cancer, including osteosarcoma. Neither the York Review nor other reviews have calculated a pooled estimate of effect; therefore it is difficult to estimate the maximum increase in risk, which is compatible with the available data. For osteosarcoma, the three small case-control studies cannot exclude an increase in risk of the order of twofold for exposure to fluoridated water, but an increase as large as this is not compatible with the ecological data, in particular those analyzed by Hoover et al. (1991). In conclusion, although a small increase in cancer risk cannot be excluded, the data do not suggest any increase in risk and in view of the type of data available it does not seem appropriate to estimate the number of cases of cancer that might be caused by fluoridation” (MRC, 2002, p. 30).

Fluoride Carcinogenicity Uncertainties

The previously discussed animal toxicological studies were equivocal. To address the uncertainty that these studies raise, the National Research Council recommended:

“...conducting one or more carefully designed analytical epidemiological (case-control or cohort) studies to more fully evaluate the relation between fluoride exposure and cancer, especially osteosarcomas, at various sites, including bones and joints. In conducting such studies, it is

important that individual exposure to fluoride from all sources be determined as accurately as possible” (NRC, 1993, p. 11).

The NHS, University of York review of human epidemiological studies regarding water fluoridation and osteosarcoma showed that the studies had weak designs and showed mixed results. The National Research Council concluded that current evidence is not sufficient to rule out a small risk of increased cancer:

“The existence of such an extensive epidemiological database on fluoride with no consistent evidence of carcinogenic effects suggests that, if there is any increase in cancer risk due to exposure to fluoride, it is likely to be small. However, most of these studies used geographic and temporal comparisons of cancer rates and hence are of limited sensitivity. Further analytical studies with accurate information on individual fluoride exposures and disease diagnoses are therefore desirable” (NRC, 1993, p. 10).

The Medical Research Council of Great Britain noted:

“The majority of information, therefore, relates to whether exposure to artificially fluoridated water for up to about 30 years may alter cancer rates, with some data for up to 35 years.... In view of this, there is a need to continue to monitor cancer rates in artificially fluoridated populations for at least 70 years after fluoridation was introduced. However, it should also be noted that studies of populations using water with naturally high fluoride levels, to which the people would have been exposed throughout their life, have not given any indication of an increase in cancer risk” (MRC, 2002 pp. 30-31).

FINDINGS: Cancer

Although a small increase in cancer risk cannot be excluded, there is no consistent evidence from human or animal studies that exposure to optimally fluoridated drinking water and other sources of fluoride causes any form of cancer in humans, including bone and joint cancer. The agreement between the epidemiological and toxicological literature reduces the uncertainty associated with any one line of evidence finding. Additional research is needed to address the remaining uncertainty whether community water fluoridation may cause cancer in humans following long-term exposures of greater than 40 years.

Bone Fractures and Osteoporosis

Two types of studies have been used to examine the possible association between bone fracture and exposure to fluoride. In the first type, clinical trials have been designed to evaluate the efficacy of fluoride in reducing fracture risk in persons with osteoporosis, a condition common in post-menopausal women in which decreased bone density can lead to fractures, especially of the spine, hip and wrist. Because fluoride increases bone density, it has been hypothesized that it might be effective as a treatment for osteoporosis. Fluoride doses in earlier studies (30-80 mg F-ion/day) were typically an order of magnitude higher than the usual exposure from drinking optimally fluoridated water. Lower levels of fluoride (9-23 mg F-ion/day that are about 4 to 10 times the average dose from dietary sources in a fluoridated community) and sustained release preparations have been used more recently. A systematic review and meta-analysis of these clinical trials was published in 2000 by researchers at the University of Ottawa (Haguenaer, Welch, Shea, Tugwell, & Wells, 2001). As summarized by the Agency for Toxic Substance and Disease Research:

“Haguenaer et al. (2000) performed a meta-analysis to examine the effects of fluoride on the treatment and prevention of post-menopausal osteoporosis using the data from the Riggs et al. (1990, 1994), Kleerekoper et al. (1991) and 10 other studies. The meta-analysis showed a significant increase in bone mineral density in the lumbar spine and hip and a decrease in bone

mineral density in the forearm after 2 or 4 years of fluoride treatment. When the data from all studies was used, fluoride treatment for 2 or 4 years did not affect the relative risk of vertebral fractures. However, studies in which the subjects were exposed to low levels of fluoride or a slow-release formulation for 4 years, a significant decrease in vertebral fracture relative risk was seen. An increase in the relative risk of nonvertebral fractures was observed when data from all studies were used; no effect was seen in studies using low levels of fluoride (<30mg/day) or slow-release fluoride” (ATSDR, 2001, p.87).

The second type of study compares fracture rates among persons or populations exposed to fluoridated and to nonfluoridated water supplies. A summary of the evidence from five “Tier One” sources (Agency for Toxic Substances and Disease Registry, NHS University of York, National Research Council, U.S. Public Health Service and the World Health Organization) follows.

The Agency for Toxic Substances and Disease Registry, stated:

“Numerous studies have examined the possible relationship between exposure to fluoride in drinking water and the risk of bone fractures. Many of these studies are ecological studies that examined communities with high level of fluoride in the water or fluoridated water” (ATSDR, 2001, p. 83).

Several prospective and retrospective studies also examined the possible association:

“These studies have found conflicting results, with studies finding a higher or lower incidence of hip fractures or no differences in hip fracture between humans exposed to fluoride in drinking water. Several studies have found decreases in hip fracture incidences in communities with fluoride in the drinking water, suggesting that there may be a beneficial effect” (ATSDR, 2001, p. 83).

The NHS Centre for Reviews at the University of York included 29 epidemiologic studies in a systematic review. Most of these studies were not statistically significant in either direction. “The statistically significant studies were evenly distributed, five indicating an increased risk of fracture and four indicating a decreased risk” (NHS, 2000, p. 53).

The National Research Council reviewed the evidence regarding fluoride exposure and risk of bone fracture:

“Of the six epidemiological studies that used geographic comparisons (where no actual intake data were available), four found a weak association between fluoride in drinking water and a small increase in the risk of hip (or other bone) fracture...and the other showed no difference in fracture risk in women who drank fluoridated or nonfluoridated water” (NRC, 1993, p. 60).

They concluded:

“In view of the conflicting results and limitations of the current data base of fluoride and the risk of hip fractures and other fractures, there is no basis at this time to recommend that EPA lower the current maximum contaminant level (MCL) of fluoride of 4 mg/L” (NRC, 1993, p. 61).

The U.S. Public Health Service reviewed the evidence that fluoride in drinking water was associated with either an increase or a decrease in bone fractures. They concluded:

“Although some epidemiologic studies have suggested that the incidence of certain types of bone fractures may be higher in some communities with either naturally high or adjusted fluoride levels, other studies have not detected increased incidence of bone fractures. However, a variety of potentially confounding factors must be examined to assess whether there is an association between exposure to fluoride and bone fractures” (USPHS, 1991, Executive Summary, p. 5).

The World Health Organization (1994) reached a similar conclusion:

“Several recent epidemiological studies of long-term exposure to fluoride in drinking-water at optimal levels for caries prevention have reached conclusions implicating fluoride as the causative factor in the increasing incidence of hip fractures in the elderly, owing to increased brittleness of the cortical bone plates. However, independent reviews of these contemporary studies conclude that they fail to establish an adequate basis for concluding that fluoride levels in drinking water are related to hip fractures and bone health (Gordon et al. 1992). Most of the studies have important limitations that restrict generalization of their results either to the population as a whole or to determining risks for individuals. Therefore no basis exists for altering current public health policy on the use of fluorides for caries prevention” (World Health Organization [WHO], 1994, p. 11).

Bone Effects Uncertainties

The uncertainty regarding the risk of bone fracture from community water fluoridation is evidenced by the summary of 29 studies reviewed by the NHS at the University of York that found 14 studies (five statistically significant) with decreased hip fractures among those living in fluoridated communities, 13 studies (four statistically significant) with increased rates of hip fractures, and three additional studies finding no association. Results of studies of other bone fractures sites were also mixed. The reviewers rated all but one of the included bone studies as having “low” validity and one as yielding “moderate” validity (NHS, 2000, p. 48). Studies of this type that compare the incidence of bone fracture across communities are subject to confounding from a number of sources as described above, including calcium levels in the water, total calcium and vitamin D intake, use of exogenous estrogens among women and individual fluoride intake.

The Medical Research Council of Great Britain identified an additional uncertainty:

“A broader consideration of the epidemiological evidence on fluoride and bone health suggests that it is of higher quality than the York Review indicates. At this stage, perhaps the most important gap in knowledge concerns the bioavailability of fluoride from different dietary sources, and in particular the influence, if any, of calcium on uptake of fluoride from drinking water ... If fluoride were shown to be much less completely absorbed from hard than soft water, the absence of an increased risk of fracture in some published studies would be less reassuring” (MRC, 2002, p. 28).

The National Research Council called for more studies of fractures that use information from individuals rather than populations.

“In these studies, it is important that individual information be collected about fluoride intake from drinking water and from all other sources, reproductive history, past and current hormonal status, intake of dietary and supplemental calcium and other cations, bone density and other factors that might influence risk of fracture” (NRC, 1993, p. 61).

Regarding research recommendations on bone effects other than fractures, the Medical Research Council of Great Britain concluded:

“There are also gaps in the evidence base on bone disorders other than fractures, only a few epidemiological studies having attempted to assess risks for any of these diseases directly. However, the gaps could only be regarded as important if there were good reasons to suspect an effect of fluoridation from our knowledge of biochemistry and toxicology” (MRC, 2002, p. 28).

FINDINGS: Bone Effects

The FTSG agrees with the conclusion of The Medical Research Council of Great Britain that states, “The possibility of an effect on the risk of hip fracture is the most important in public health terms. The available evidence on this suggests no effect, but cannot rule out the possibility of a small percentage change (either an increase or a decrease) in hip fractures” (Medical Research Council, 2002, p. 3).

Skeletal Fluorosis

When ingested in large doses for an extended period of time, fluoride results in thickened bones and exostoses (skeletal fluorosis). According to the Agency for Toxic Substances and Disease Registry:

“Signs of skeletal fluorosis range from increased bone density to severe deformity, known as crippling skeletal fluorosis.... Reported cases are found almost exclusively in developing countries, particularly India, and are associated with malnutrition (Pandit et al. 1940). Tea consumption and high water intake due to tropical climate are probably also contributing factors.... It is generally stated that a dose of 20-80 mg/day (equivalent to 10 to 40 ppm in the water) is necessary for the development of crippling skeletal fluorosis (NAS 1971a), but individual variation, variation in nutritional status, and the difficulty of determining water fluoride levels in such situations make it difficult to determine the critical dose.

A study of 116 people who had lived in an area with an average of 8 ppm fluoride in the drinking water for at least 15 years found a 10-15% incidence of fluoride-related bone changes (Leone et al. 1995). Coarsened trabeculation and thickened bone were observed, but no exostoses were evident, and the subjects were asymptomatic” (ATSDR, 2001, p. 82).

Approximately 50% of ingested fluoride is excreted by the kidneys within 24 hours, a small amount is stored in the teeth, and the rest is mainly deposited in the skeleton (The Lord Mayor’s Taskforce on Fluoridation, 1997, p. 51). Over time, excessive levels of fluoride can produce abnormalities in bone, if dose and duration are great enough. As shown in Table 6, these abnormalities become detectable on x-rays, and rarely can result in a clinical syndrome of skeletal fluorosis). Table 6 shows the pre-clinical (asymptomatic) and clinical stages of skeletal fluorosis along with the most common symptoms. The amount of fluoride accumulation in the bone tissue of subjects in each stage is also given. One study found a linear relationship between the concentration of fluoride in bone at autopsy in adult humans and the concentration of fluoride in their drinking water (ranging from 0.1 to 4 ppm). “Average fluoride levels in the iliac crest bone ash in people with drinking water fluoride levels of ≤ 0.3 , 1 and 4 ppm were 700, 2,300, and 6,900 ppm, respectively” (ATSDR, 2001, p. 123, citing Zipkin et al. 1958).

Table 6

Preclinical and Clinical Stages of Human Skeletal Fluorosis and Correlation to Bone Ash Fluoride Concentration

(adapted from Table 23, USPHS 1991, p. 46)

Osteosclerotic Phase	Ash Concentration ¹ (mg F/Kg)
Normal Bone	500-1,000
<u>Preclinical Phase</u> Asymptomatic; slight radiographically-detectable increase in bone mass	3,500-5,000
<u>Clinical Phase I</u> Sporadic pain; stiffness of joints; osteosclerosis of pelvis & vertebral column	6,000-7,000
<u>Clinical Phase II</u> Chronic joint pain; arthritic symptoms; slight calcification of ligaments; increased osteosclerosis/cancellous bones; with/without osteoporosis of long bones	7,500-9,000
<u>Phase III: Crippling Fluorosis</u> Limitation of joint movement; calcification of ligaments/neck, vertebral column; crippling deformities. spine & major joints; muscle wasting; neurological defects/compression of spinal cord	>8,400

¹ Ash concentration is the amount of fluoride per weight of bone ash, usually measured from a sample of bone from the iliac crest

The concentration of fluoride also increases with age. A study cited by Agency for Toxic Substances and Disease Registry (2001) examined fluoride bone ash concentrations in five people between 64 and 85 who had lived in an area with water containing 1mg/L fluoride for at least 10 years. Their average bone fluoride concentration was 2,250 mg F/Kg (ATSDR, 2001, p. 82). Note that the level of fluoride per weight of bone ash in long-term residents of fluoridated communities is above the level in "normal bone" but below the level at which changes can be identified on x-rays, and well below the levels at which symptoms of skeletal fluorosis begin to appear.

According to a U.S. Public Health Service Committee, "The total quantity of fluoride ingested is the single most important factor in determining the clinical course of skeletal fluorosis (Krishnamachari, 1986); the severity of symptoms correlates directly with the level and duration of exposure (Fischer, et al., 1989)" (USPHS, 1991, p. 45). However there appear to be other important cofactors that render individuals susceptible to this disease since, "crippling skeletal fluorosis continues to be extremely rare in the United States...even though for many generations there have been communities with drinking water fluoride concentrations in excess of those that resulted in this condition in other countries (Singh and Jolly, 1970)" (IOM, 2000, p. 308).

The National Research Council made the following observations concerning skeletal fluorosis in their review:

"Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years. During the last 30 years, only five cases have been reported in the United States. The history of fluoride intake for two of the cases was determined with reasonable accuracy (Sauerbrunn et al., 1965; Goldman et al., 1971). The individuals consumed up to 6 L of water per day containing fluoride at 2.4-3.5 mg/L in one case and 4.0-7.8 mg/L in the other. The

daily fluoride intake was estimated at 15-20 mg for 20 years. In general, this intake would be associated with a drinking-water supply containing fluoride at about 10 mg/L².

Thus, crippling skeletal fluorosis in the United States has been rare and not a public health problem (Leone et al., 1954; Stevenson and Watson, 1957), even though for many generations there have been communities with drinking water fluoride concentrations in excess of those that have resulted in the condition in other countries (Singh and Jolly, 1970). The puzzling geographic distribution of the disorder usually is ascribed to unidentified dietary factors that render the skeleton more or less susceptible.

The small number of cases of skeletal fluorosis in the United States has ruled out the possibility of systematic epidemiological evaluation. Based on limited data in the literature on skeletal fluorosis, the subcommittee [National Research Council] concludes that skeletal fluorosis is not a public health issue in the United States” (NRC, pp. 59-60).

The Locker review conducted for the Ontario Ministry of Health (1999) reported:

“Most estimates indicate that crippling fluorosis is associated with chronic fluoride exposures of ≥ 10 mg/day for at least ten years. These exposures occur as either endemic (exposure to the naturally fluoridated drinking water) or industrial (e.g. exposure to the cryolite dust) (Fejerskov, 1996; Whitford, 1996). Beside the dose and duration of fluoride exposure, the development of skeletal fluorosis is influenced by various other factors. The most common are age, physical activity, kinetics of bone remodeling, nutritional status and renal insufficiency. Epidemiological studies of bone mineral density have not detected changes consistent with skeletal fluorosis resulting from the consumption of drinking water containing fluoride at the concentrations considered optimal for caries prevention” (Locker, 1999, p. 44).

Skeletal Fluorosis Uncertainties

According to the Agency for Toxic Substances and Disease Registry, “The incidence of skeletal fluorosis in the United States is unknown, since it appears that the early signs can only be identified radiologically” (ATSDR, 2001, p. 82).

Three members (GM, EC, RN) of the FTSG were concerned that the studies on skeletal fluorosis estimated the likelihood of occurrence based on a dosage of 10-20 mg of fluoride per day over at least 10-20 years, but there was limited data regarding the likelihood of occurrence based on a cumulative dose over a lifetime of exposure. This was particularly concerning to them given the fact that fluoride accumulates in the bone. Skeletal fluorosis is rarely reported in the United States. Because the symptoms of clinical non-crippling stages of skeletal fluorosis (pain in the bones and joints, muscle weakness, fatigue, calcification of ligaments and bone spurs) two FTSG members (GM, EC) wondered if these symptoms could be misdiagnosed, resulting in under-reporting among susceptible individuals living in communities with optimally fluoridated drinking water (e.g. persons with long-term nutritional deficiencies such as deficiencies of protein, calcium, magnesium, and/or vitamin C and people with chronic kidney failure).

² Approximately 10 times the concentration in Fort Collins water.

FINDINGS: Skeletal Fluorosis

At the concentrations of fluoride provided in Fort Collins water including exposures from all sources over a lifetime, skeletal fluorosis caused by drinking water exposure is not likely to be a health issue. The available data are not consistent with a likelihood of increased human skeletal fluorosis from city water fluoridation.

Additional research is needed to reduce the remaining uncertainty if cumulative exposure to all sources of fluoride (including drinking water fluoride at levels of 1 mg/L) over a lifetime may lead to pre-clinical or milder forms of skeletal fluorosis in some sensitive populations.

Dental Enamel Fluorosis

A summary of the issue concerning enamel fluorosis and water fluoridation is found in the report from the Centers for Disease Control and Prevention, *Recommendations for using fluoride to prevent and control dental caries in the United States* (2001):

“Fluoride ingested during tooth development can also result in a range of visually detectable changes in enamel opacity (i.e., light refraction at or below the surface) because of hypomineralization. These changes have been broadly termed enamel fluorosis, certain extremes of which are cosmetically objectionable (49). (Many other developmental changes that affect the appearance of enamel are not related to fluoride (50).) Severe forms of this condition can occur only when young children ingest excess fluoride, from any source, during critical periods of tooth development. The occurrence of enamel fluorosis is reported to be most strongly associated with cumulative fluoride intake during enamel development, but the severity of the condition depends on the dose, duration, and timing of fluoride intake. The transition and early maturation stages of enamel development appear to be most susceptible to the effects of fluoride (51); these stages occur at varying times for different tooth types. For central incisors of the upper jaw, for example, the most sensitive period is estimated at age 15-24 months for boys and age 21-30 months for girls (51,52).

Concerns regarding the risk for enamel fluorosis are limited to children aged ≤ 8 years; enamel is no longer susceptible once its pre-eruptive maturation is complete (11). Fluoride sources for children aged ≤ 8 years are drinking water, processed beverages and food, toothpaste, dietary supplements that include fluoride (tablets and drops), and other dental products.

The very mild and mild forms of enamel fluorosis appear as chalklike, lacy markings across a tooth's enamel surface that are not readily apparent to the affected person or casual observer (53). In the moderate form, $>50\%$ of the enamel surface is opaque white. The rare, severe form manifests as pitted and brittle enamel. After eruption, teeth with moderate or severe fluorosis might develop areas of brown stain (54). In the severe form, the compromised enamel might break away, resulting in excessive wear of the teeth. Even in its severe form, enamel fluorosis is considered a cosmetic effect, not an adverse functional event. (8, 11, 55, 56)

When enamel fluorosis was first systemically investigated during the 1930s and 1940s, its prevalence was 12%-15% for very mild and mild forms and zero for moderate and severe forms among children who lived in communities with drinking water that naturally contained 0.9-1.2 ppm fluoride (53). Although the prevalence of this condition in the United States has since increased (8, 58, 59), most fluorosis today is of the mildest form, which affects neither cosmetic appearance nor dental function. The increased prevalence in areas both with and without fluoridated community drinking water indicates that, during the first 8 years of life (8), the total intake of fluoride from all sources has increased for some children (Centers for Disease Control and Prevention [CDC], 2001, pp. 6-7).

(8, 11, 49, 50, 51, 52, 53, 54, 55, 56,58, 59) References within a quote are available in the source document.

The Medical Research Council of Great Britain adds the following terminology, “Dental fluorosis is a form of developmental defect of tooth enamel. Histologically it presents as hypocalcification, while clinically it ranges from barely visible white striations on the teeth through to gross defects and staining of the enamel” (MRC, 2002, p.19).

Prevalence of Enamel Fluorosis in the U.S.

The U.S. Centers for Disease Control and Prevention reviewed the most recent national estimates of the prevalence of fluorosis:

“The 1986-1987 National Survey of Dental Caries in U.S. School Children (the most recent national estimates of enamel fluorosis prevalence) indicated that the prevalence of any enamel fluorosis among children was 22%-23% (range 26% of children aged 9 years to 19% of those aged 17 years (60, 61). Almost all cases reported in the survey were of the very mild or mild form, but some cases of the moderate (1.1%) and severe (0.3%) forms were observed” (CDC, 2001, pp. 8-9).

The estimates cited above were averages across all communities, ranging from very low to very high levels of fluoride. “In communities with drinking water containing 0.7-1.2 ppm fluoride, the prevalence was 1.3% for the moderate form of enamel fluorosis and zero for the severe form; thus, few cases of enamel fluorosis were likely to be of cosmetic consequence (8,61)” (CDC, 2001, p. 12).

According to a recent study, the mean prevalence of dental fluorosis, relative to Dean’s original data, has increased by 39% in optimally fluoridated areas and by 91% in nonfluoridated areas (Pendry & Stamm, 1990, cited in Lewis & Banting, p. 156).

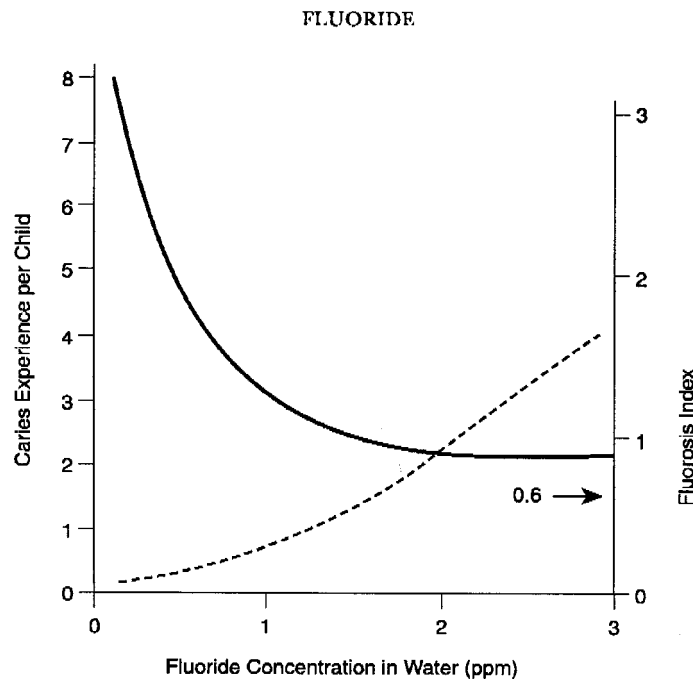


Figure 1. Taken from Figure 8-1, page 299, of the Committee on the Scientific Evaluation of Dietary Reference Intakes, Food & Nutrition Board, Institute of Medicine (2000)

Relationships among caries experience (solid line), dental fluorosis index (dashed line), and the fluoride concentration of drinking water. A fluorosis index value of 0.6 was judged to represent the threshold for a problem of public health significance. The data are based on the examination of 7,257 12-to 14-year old children (Dean, 1942).

(8, 60, 61) References within a quote are available in the source document.

As demonstrated in the total exposures section earlier in this finding, total exposures have increased and at optimal levels of water fluoridation are higher than shown in Figure 1 above.

The NHS Review at the University of York found that at a fluoride level of 1 ppm an estimated 12.5% of exposed people would have fluorosis that they would find aesthetically concerning" (NHS, 2000, p. xiii). The NHS Review looked at 88 studies of dental fluorosis:

“All of the studies were of evidence level C (lowest quality), except one level B. From these models, the pooled estimate of the prevalence of fluorosis at a water fluoride concentration of 1.0 ppm was 48%...and for fluorosis of aesthetic concern 12.5%” (NHS, 2000, p. 45).

Contribution of CWF to Enamel Fluorosis

Only a fraction of current levels of fluorosis in a fluoridated community like Fort Collins can be attributed to drinking optimally fluoridated water. In the context of multiple sources of ingested fluoride, how much does water fluoridation at optimal levels contribute to the overall prevalence of fluorosis? There are two lines of reasoning that have been used to answer this question. The first is to use levels of fluorosis in studies conducted in communities before fluoride was present in the diet, bottled waters, and dental products as an estimate of what water fluoride contributes. The National Research Council follows this line of reasoning with the following:

“In general, the evidence supports the conclusion that fluoridation at the recommended concentrations, in the absence of fluoride from other sources, results in a prevalence of mild-to-very mild (cosmetic) dental fluorosis in about 10% of the population and almost no cases of moderate or severe dental fluorosis. At five or more times the recommended concentration, the proportion of moderate-to-severe dental fluorosis is substantially higher” (NRC, 1993, p. 5).

A second approach is to compare relative levels of fluorosis in communities with and without fluoridated water. Lewis and Banting (1994) and the NHS Center for Reviews and Dissemination at the University of York (2000) conducted reviews and synthesis of the literature regarding fluorosis. Both reviews found that the risk of fluorosis has increased in both optimally fluoridated (1.0 mg/L) and low-fluoride communities (0.4 mg/L), with the absolute difference in prevalence of fluorosis remaining stable at about 15%. Lewis and Banting estimated that the percent of fluorosis attributable to water fluoridation dropped from nearly 100% in the 1940s to 40% in the early 1990s. The remaining 60% was attributed to increased use of fluoride dental products and to the “halo effect” (Lewis & Banting, 1994, p. 156).

Other Contributing Causes of Enamel Fluorosis

A large number of studies have reported an association between fluoride supplement use and enamel fluorosis (NRC, 1993 p. 43). In response to accumulated evidence the supplement dosage schedule for children nine and younger was markedly reduced in the U.S. in 1994. Levy and Muchow (1992) and Pendrys and Morse (1990) are among those who documented that improper dosing of supplements is common and that inappropriate use of fluoride supplements in children living in fluoridated communities is an important cause of fluorosis. Swallowing of toothpaste by preschool children and prolonged use of powdered infant formula in fluoridated communities have been identified as risk factors for fluorosis as well (NRC, 1993, pp. 311-312; CDC, 2001, pp. 11-12). Several studies have attempted to estimate the relative impact of specific fluoride sources on the prevalence of enamel fluorosis in the U.S. and Canada (Pendrys, Katz, & Morse, 1994; Osuji, et al., 1988; Pendrys, 2000). Pendrys (2000) reported findings from a study of 663 middle school students:

“In the nonfluoridated study sample, sixty-five percent of the enamel fluorosis cases were attributed to fluoride supplementation under the pre-1994 protocol. An additional 34 percent were explained by the children having brushed more than once per day during the first two years of

life. In the optimally fluoridated study sample, 68 percent of the enamel fluorosis cases were explained by the children using more than a pea-sized amount of toothpaste during the first year of life, 13 percent by having been inappropriately given a fluoride supplement, and 9 percent by the use of infant formula in the form of a powdered concentrate” (Pendry, 2000, p. 746).

The Institute of Medicine committee report on dietary reference intakes (1997) concluded that intakes of fluoride from water and diet have remained about the same since the 1940s, so that, in optimally fluoridated communities, “...the additional intake by children at risk of enamel fluorosis almost certainly derives from the use of fluoride-containing dental products” (IOM, 2000, p. 312).

Using the National Research Council’s logic in estimating fluorosis rates attributable to community water fluoridation in the absence of other fluoride sources, the 12-15% prevalence of dental fluorosis that existed in optimally fluoridated communities before the introduction of other fluoride sources can be thought to be the amount of current fluorosis due to drinking Fort Collins water. Given that, as many as 160-200 children in Fort Collins may develop enamel fluorosis in their permanent teeth annually that may be statistically attributable to consumption of community fluoridated water, all of it of the very mild or mild form³. This estimate theoretically represents the amount and severity of fluorosis that would be averted by suspending water fluoridation. Many more children, not so easily determined, may develop dental fluorosis from incorrectly using fluoridated dental products such as ingesting toothpaste or taking fluoride supplements on a regular basis, between the ages of four months and eight years. Fluorosis attributable to these sources would not be expected to decrease if Fort Collins suspended water fluoridation. Although moderate to severe enamel fluorosis is not caused by community water fluoride at 1 ppm by itself, some reduction in the incidence of moderate to severe fluorosis from exposure to all sources of fluoride would be expected if community water fluoridation were eliminated.

Given the availability and indiscriminate use of fluoridated dental products, children in the vulnerable ages in both fluoridated and nonfluoridated communities may be exposed to excessive amounts of fluoride. The Canadian city of Calgary came to the following conclusion regarding the problem of enamel fluorosis among children:

“The Panel recommends that health authorities pay more attention to identifying uncontrolled sources of fluoride, especially due to children swallowing high fluoride toothpaste. Reducing uncontrolled sources of fluoride would be a more effective means of reducing dental fluorosis than eliminating fluoridation of water” (Expert Panel for Water Fluoridation Review, City of Calgary, 1998, p. 30).

The Center for Disease Control and Prevention recommends that the medical and dental communities and the media educate the public about the potential for increasing the prevalence and severity of enamel fluorosis if children consuming fluoridated water are treated with fluoride supplements or consume excessive amounts of fluoridated toothpaste (CDC, 2001, p. 26).

Dental Fluorosis Uncertainties

Uncertainties identified by the FTSG (or specific members):

- The current prevalence of dental fluorosis in fluoridated and nonfluoridated communities in our region is unknown.
- The public’s perceptions regarding the aesthetic acceptability or lack of acceptability of mild to moderate dental fluorosis is unknown.

³ The average number of children in each age of life between 4 months and 8 years in Fort Collins is about 1350 according to 2000 U.S. Census data. The prevalence of fluorosis measured in the early community fluoridation trials was 12%-15% all the very mild to mild forms. Therefore, $(1350) \times (12\% \text{ to } 15\%) = 162 \text{ to } 203$ children per year may develop fluorosis.

- It is not known whether the prevalence of dental fluorosis would decrease or increase if Fort Collins were to suspend water fluoridation.

FINDINGS: Dental Fluorosis

At the concentrations of fluoride provided in Fort Collins water, in combination with other sources of fluoride, as many as one in four children under age eight may develop very mild to mild dental fluorosis. This degree of fluorosis may or may not be detectable by the layperson. With oral health as the goal, this degree of dental fluorosis is considered an acceptable adverse effect given the benefits of caries prevention. Since about 60% of dental fluorosis can be attributed to other sources of fluoride (particularly toothpaste and other dental products) parental supervision over tooth paste swallowing in their young children and proper prescribed supplementation in infants will likely reduce development of enamel fluorosis more than the removal of added fluoride in drinking water.

Thyroid Function

Questions raised at the public meeting about the potential for thyroid impacts from drinking water fluoridation led the FTSG to inquire about studies of the relationship between fluoride intake and thyroid function. Some at the public meeting pointed out that fluoride had been used to treat hyperthyroidism and questioned whether drinking water fluoridation would exacerbate hypothyroidism.

Staff pursued this question and produced 25 abstracts and some information from the “Tier One” literature for FTSG review and discussion. The literature search included an extensive search of the *National Library of Medicine Database* as well as *Medline* and all major biomedical databases available through the Colorado State University Morgan Library and the University of Colorado Health Sciences Center Dennison Library. See reference list in Appendix A.

Of most relevance and therefore having the greatest impact on the FTSG findings are three publications. Eichner, Borner, Henschler, Kohler, and Moll (1981) examined 26 women who received 40 mg of sodium fluoride twice a day (equivalent 36 mg of fluorine) for three to six months as a treatment for osteoporosis. In a second study published separately by two different lead authors, Hasling, Nielsen, Melsen, and Mosekilde (1987) and Mosekilde, Charles, Eriksen, Hasling, and Melsen (1986), described 163 patients treated for eight years (total of 460 patient years) with a combination of sodium fluoride (60 mg/day), calcium phosphate (45 mmol/day) and vitamin D2 (18,000 IU/day). Both cited studies found no change in thyroid function.

Thyroid Uncertainties

There were some studies identified in the FTSG’s literature search that suggested a deleterious effect on the thyroid by fluoride. While these studies were considered to be of lower quality or relevance, two members of the FTSG held that there remains uncertainty regarding the effect of fluoride on thyroid structure and function. The Medical Research Council commented:

“The York review listed three studies in which goiter was the outcome of interest. Two of these studies (Gedalia & Brand, 1963; Jooste et al., 1999) found no significant association with water fluoride level. The third (Lin et al., 1991) found a significant positive association between combined high fluoride/low iodine levels and goiter. However, because this study looked at combined fluoride/iodine uptakes, and has not been published in a peer reviewed journal, the findings should be treated cautiously. Further work on this aspect is of low priority” (MRC, 2002, p. 34).

FINDINGS: Thyroid Effects

In the literature reviewed, doses appropriate for caries reduction were not shown to negatively impact thyroid function. Studies in which humans received doses significantly higher than the optimum fluoride intake for long periods of time showed no negative impact on thyroid function. For those with hypothyroidism, the risks of alteration of thyroid structure or function are very low. The absence of our finding any conclusive evidence that drinking water fluoride exposures causes increased risk to thyroid function does not prove that fluoride can not affect thyroid function. The available data are consistent with a finding of a low likelihood of risk to human thyroid function from water fluoridation.

Immune System Effects

Potential immune system effects are of two types—hypersensitivity (allergic) reactions and immunotoxicity effects (weakening of the immune system). Information on both is limited.

With respect to allergic reactions, the Medical Research Council of Great Britain notes:

“Information regarding the allergic potential of fluoride in drinking water is sparse. A paper by Spittle (1993) concluded that some individuals exhibit an allergic/hypersensitivity reaction to fluoride, but reviews by NRC (1993), NHMRC (1991) and Chalacombe (1996) all concluded that the studies undertaken do not support claims that fluoride is allergenic. They considered the weight of evidence to show that fluoride is unlikely to produce hypersensitivity or other immunological effects” (MRC, 2002, p. 32).

The U.S. Public Health Service (1991) and the National Research Council (1993) both concluded the following:

“The literature pertaining to immunological effects of fluoride is limited. Although direct exposure to high concentrations of sodium fluoride in vitro affects a variety of enzymatic activities, the relevance of the effects in vivo is unclear. Standardized immunotoxicity tests of sodium fluoride at relevant concentrations and routes of administration have not been conducted. The weight of evidence shows that fluoride is unlikely to produce hypersensitivity and other immunological effects” (NRC, 1993, p. 9; USPHS, 1991, p. 70).

Immunological System Effects Uncertainties

The Medical Research Council noted the sparse amount of evidence regarding adverse effects to the human immune system. They concluded that, “There is no information on the immunotoxicity of fluoride. Further work in this area would be useful, but in the absence of obvious toxic mechanisms for such an effect is considered to be of low priority” (MRC, 2002, p. 32).

With respect to immunotoxicity effects, one FTSG member submitted a paper entitled *Is the Ingestion of Fluoride an Immunosuppressive Practice?* that cites several *in vitro* observations to suggest that, “the habitual ingestion of small doses of fluoride, even as small as the 1 mg/L contained in fluoridated water, may decrease the function of the immune system” (Sutton, 1991).

FINDINGS: Immunological Effects

Overall, evidence is lacking that exposure to fluoride through drinking water causes any problems to the human immune system. The absence of our finding any conclusive evidence that drinking water fluoride exposures causes increased risk to human immune system function does not prove that fluoride is harmless to the human immune systems.

Other Potential Health Effects

The potential for associations between a number of other potential adverse health effects and exposure to fluoridated water has been explored in many epidemiologic and toxicological studies and summarized in reviews conducted by the Agency for Toxic Substances and Disease Registry, the World Health Organization, the National Research Council of the National Academy of Science, and the U.S. Public Health Service. The following areas have been studied:

- Effects of fluoride on the renal system
- Effects of fluoride on the gastrointestinal system
- Effects of fluoride on hypersensitivity and the immune system (described above)
- Effects of fluoride on reproduction
- Genotoxicity
- Developmental effects including birth defects and Down Syndrome
- Effect of fluoride on all-cause mortality

As in the above sections, relevant citations from the texts of these reviews follow; a fuller description of each is found in Appendix 2 to this document.

The National Research Council of the National Academy of Sciences came to the following conclusion on these issues:

“The subcommittee concludes that available evidence shows that the threshold dose of fluoride in drinking water for renal toxicity in animals is approximately 50 mg/L. The subcommittee therefore believes that ingestion of fluoride at currently recommended concentrations is not likely to produce kidney toxicity in humans.... The subcommittee concludes that the available data show that the concentrations of fluoride found in drinking water in the United States are not likely to produce adverse effects in the gastrointestinal system.... The weight of evidence shows that fluoride is unlikely to produce hypersensitivity and other immunological effects.... The subcommittee concludes that the fluoride concentrations associated with adverse reproductive effects in animals are far higher than those to which human populations are exposed. Consequently, ingestion of fluoride at current concentrations should have no adverse effects on human reproduction.... The subcommittee concludes that the genotoxicity of fluoride should not be of concern at the concentrations found in the plasma of most people in the United States.... Based on its review of available data on toxicity of fluoride, the subcommittee concludes that EPA’s current MCL of 4 mg/L for fluoride in drinking water is appropriate as an interim standard” (NRC, 1993, pp. 7-11).

The U.S. Public Health Service concluded in 1991:

“Chronic low-level exposure of healthy individuals does not appear to present problems in other organ systems, such as the gastrointestinal, the genitourinary, and the respiratory systems.... Chronic low level fluoride exposure is not associated with birth defects. Studies also fail to establish an association between fluoride and Down Syndrome. Genotoxicity studies of fluoride, which are highly dependent on the methods used, often show contradictory findings. The most

common finding is that fluoride has not been shown to be mutagenic in standard tests on bacteria (Ames Test). In some studies with different methodologies, fluoride has been reported to induce mutations and chromosome aberration in cultured rodent and human cells. The genotoxicity of fluoride in humans and animals is unresolved despite numerous studies” (USPHS, 1991, pp. 87 & 89).

Uncertainties Regarding Other Health Effects

Several other adverse effects have been proposed as being associated with elevated with fluoride intake. They include:

- Effects on the pineal gland
- Senile dementia
- Age at menarche
- Anemia during pregnancy
- Sudden infant death syndrome
- Primary degenerative dementia
- Reduced intelligence and other central nervous system effects
- The possibility that fluoride added to water could influence toxicity from other substances (i.e., by causing leaching of aluminum from cookware or affecting the uptake or bioavailability of toxic substances such as aluminum and lead in the gut)

The Medical Research Council of Great Britain as well as the Agency for Toxic Substances and Disease Registry found the available information on these effects to be limited and inconclusive. The Medical Research Council noted, “Further targeted research may be warranted, but this is presently of low priority unless and until critical literature reviews are undertaken that demonstrate specific research needs” (MRC, 2002, p. 34).

Fluoride and Blood Lead Levels

The concern regarding the possible association between blood lead levels and the use of hydrofluorosilicic acid (HFS) is considered in Finding #4. Two recent ecological studies found a significant association between community average blood lead levels in children residing in areas with water fluoridated using HFS, compared to those residing in communities fluoridated with sodium fluoride, or not fluoridated (Masters & Coplan, 1999; Masters, Coplan, Hone, & Dykes, 2000). According to the U.S. Environmental Protection Agency, there is no reliable evidence to suggest that this fluoridation agent may increase blood lead levels. The Medical Research Council of Great Britain concludes, “This appears to be a controversial area and further studies are awaited” (MRC, 2002, p. 36). The National Toxicity Program recently nominated the use of HFS as a fluoridation agent for a formal review.

Sensitive Populations

The Agency for Toxic Substances Disease Registry toxicological profile identified the following populations as potentially exhibiting a different or enhanced response to fluoride exposure.

“Existing data indicate that subsets of the population may be unusually susceptible to the toxic effects of fluoride and its compounds. These populations include the elderly, people with deficiencies of calcium, magnesium, and/or vitamin C, and people with cardiovascular and kidney problems. However, these effects would not be expected at typical exposure levels (at 1 ppm fluoride)” (ATSDR, 2001, p. 143).

FINDINGS: Other Health Effects

The potential for other health effects was reviewed by the FTSG. There was not adequate evidence to consider any of these other potential adverse effects a concern with respect to fluoridation of Fort Collins water supplies. The absence of our finding any conclusive evidence that drinking water fluoride exposures causes other potential health effects does not prove that fluoride can not cause other potential health effects.

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