APPENDIX A

Review of the U.S. National Research Council Report:

Fluoride in Drinking Water

A Scientific Review of EPA's Standards

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A. INTRODUCTION

This document was prepared in response to a request to provide a review of the United States National Research Council of the National Academies 2006 report entitled "Fluoride in Drinking Water, A Scientific Review of EPA's Standards" (subsequently referred to as the National Research Council report). The National Research Council was asked to prepare their report by the U.S. Environmental Protection Agency (EPA) which is required to periodically review exposure to contaminants in drinking water under that country's Safe Drinking Water Act. The National Research Council report was intended to assess the maximum contaminant level (MCL) and secondary maximum contaminant level (SMCL) for naturally-occurring fluoride in drinking water in the United States.

It is very important to note that the National Research Council report was not intended to address drinking water where fluoride is added to prevent tooth decay. The report explicitly states that "this report does not evaluate nor make judgments about the benefits, safety, or efficacy of artificial water fluoridation"[1]. In the United States (U.S.), the current recommended levels for adjusting fluoride in drinking water are between 0.7 and 1.2 mg/L[2]. In Canada, the optimal concentration of fluoride in drinking water to promote dental health is set at 0.7 mg/L[3]. Health Canada is also preparing the final version of a report that will assess the Maximum Acceptable Concentration (MAC) for fluoride in drinking water in Canada which is set at 1.5 mg/L. A draft of the Canadian report[4] closed for public comment in November 2009 and the final version is expected shortly.

The maximum contaminant level (MCL) in the United States is to be as close to the level where no adverse health effects are expected to occur with a margin of safety that is considered "adequate". In the U.S., the maximum contaminant level for fluoride was set at 4 mg/L in 1984 in order to prevent crippling fluorosis from fluoride intake. The secondary maximum contaminant level (SMCL) is 2 mg/L and it was set to prevent objectionable tooth enamel fluorosis. At levels above 4 mg/L, naturally fluoridated water would not be considered a safe source of drinking water. At levels between 2 and 4 mg/L, a notice about the potential risk for enamel fluorosis must be sent to the people drinking the water.[5] In Ontario, local public health units are required to raise public and professional awareness to control excess exposure from other sources when naturally-occurring fluoride levels in drinking water are between 1.5 mg/L and 2.4 mg/L[6]. In the Village of Thorndale, where naturally-occurring fluoride levels occasionally exceed 1.5 mg/L, annual notices accompany water bills that are sent directly to all water customers.

The National Research Council report was prepared by a committee specifically convened for this review entitled the "Committee on Fluoride in Drinking Water". The Committee consisted of 12 members including dentists, physicians, epidemiologists, toxicologists and other scientists, with varying views on water fluoridation. The Committee reviewed information related to fluoride with a focus on research since 1993, since research published prior to this time period had been covered in a previous National Research Council report. The Committee heard presentations from many

sources and reviewed published research articles, literature reviews, position papers and unpublished data[7].

The Summary of the National Research Council report is provided in Appendix A. It provides an overview of the findings of the report. The full report, including references and appendices, is over 500 pages long and can be found at http://books.nap.edu/catalog.php?record_id=11571 .

This review document will provide background information to assist in understanding the fluoride values, epidemiologic studies and statistics used in the National Research Council report. Section D will review the information provided in the various chapters of the National Research Council report that discuss fluoride and specific body systems. For each chapter, the information in the report will be briefly summarized and additional information and context will be added with regard to the potential implications from adjusted fluoride in London's drinking water. Three communities in Middlesex County (Arva, Ballymote and Delaware) also receive drinking water to which fluoride is added. As this water is provided from the City of London's system, this document will only make reference to the City of London's drinking water supply.

B. INTERPRETING THE NUMBERS

The following provides an overview of the numbers that are commonly encountered in the National Research Council report and in other information related to fluoride.

B.1 Fluoride in drinking water

IMPORTANT POINT
Target for fluoridation of London's drinking water: 0.7 mg/L (or ppm)

Fluoride in drinking water is expressed in "milligrams per litre (mg/L)" which is the same as "parts per million (ppm)". It is easiest to understand as mg/L. As an example, the target for fluoridating drinking water in London is set at 0.7 mg/L. This means that a person who drinks 1 litre of water will consume 0.7 milligrams (mg) of fluoride. Table 1 outlines some of the commonly referred to fluoride parameters related to drinking water.

Table1. Commonly referred to fluoride parameters related to drinking water

Level	Significance	Comments
0.7 mg/L	Target level for adjusting fluoride in London's drinking water. Optimal concentration of fluoride in drinking water to promote dental health in Canada.	Typical water consumption in the US is estimated at approximately 1 litre per day[8]. Assuming this is the same in London, 0.7 mg of fluoride will typically be consumed from fluoridated water per day. In the U.S. it is estimated that 90% of people drink approximately 2 litres or less of water per day[9]. Assuming this is the same in London, 90% of people will consume 1.4 mg or less of fluoride from drinking water per day.
0.7 to 1.2 mg/L	Current target level for adjusting fluoride in drinking water in the U.S.	New recommendation to reduce the target level to 0.7 mg/L have been recently proposed[10].
1.5 mg/L	Maximum Acceptable Concentration (MAC) for natural fluoride levels in drinking water in Canada.	When naturally-occurring fluoride levels are between 1.5 and 2.4 mg/L, consumers and professionals in Ontario must be advised of the possible risk of dental fluorosis and measures to be taken to reduce this risk.
2 mg/L	Secondary maximum contaminant level in the U.S.	When naturally-occurring fluoride levels are between 2 and 4 mg/L, consumers in the U.S. must be advised of the possible risk of dental fluorosis and the measures to be taken to reduce this risk.
4 mg/L	Maximum contaminant level in the U.S.	When naturally-occurring fluoride levels exceed 4 mg/L, this water should not be used as a source of drinking water.

B.2 Daily intake of fluoride from all sources

Health Canada produced an estimate of tolerable daily intake to prevent moderate and severe dental fluorosis in those who are most vulnerable (children 1 – 4 years of age). The tolerable daily intake was estimated to be 0.105 mg/kg/day (milligram per kilogram per day)[11] (also expressed as 105 μg/kg/day – micrograms per kilogram per day). Using this estimate of 0.105 mg/kg/day, a child weighing 13 kg can consume 1.37 mg of fluoride per day without a risk of moderate dental fluorosis. Only children less than 6-8 years of age are at risk for dental fluorosis, since this is when the permanent teeth are forming, with 22 – 26 months being the period of maximum risk for the front teeth[12].

The tolerable daily intake estimate of 0.105 mg/kg/day is consistent with the U.S. Institute of Medicine's tolerable upper intake of 0.1 mg/kg/day for children ages 0 – 8 years[13] [14]. Others have used estimates of 0.05-0.07 mg/kg/day to maximize the prevention of cavities and minimize enamel fluorosis[15] and this range of values is used as a reference point in the National Research Council report.

Health Canada has estimated a tolerable daily intake of fluoride from all sources of:

- 0.105 mg/kg/day (105 μg/kg/day)
    - For a 13 kg child = 1.37 mg/day of fluoride
    - For a 70 kg person = 7.35 mg/day of fluoride

      The average adult consumes about 0.04 mg/kg/day[a] of fluoride from all sources which is 2.8 mg/day of fluoride.

[a] National Research Council. Page 63

Estimated daily intake of fluoride from all sources includes fluoride from water, toothpaste, food and beverages and dental supplements. Various estimates of daily intake are produced in the National Research Council report depending on the concentration of fluoride in the drinking water, the amount of water consumed each day, the amount of fluoride estimated to be in other foods and beverages consumed in areas where the water is fluoridated, and whether fluoride supplements are used.

Table 2 provides some of the daily intake estimates produced in the National Research Council report assuming 1.0 mg/L in drinking water (which is the closest to but exceeds London's water concentration) and no fluoride supplements (which are not recommended in London)[16]. Because Table 2 is based on 1.0 mg/L of fluoride in drinking water and not 0.7 mg/L as in London's water, the daily intake estimates in Table 2 are higher than would be experienced from drinking London's water.

Using a cut off of 0.05-0.07 mg/kg/day for optimal daily intake (as was used in the National Research Council report), the estimated daily intake will be exceeded for non-nursing infants using all methods of calculating daily water intake. Using the tolerable daily intake of 0.105 mg/kg/day (as proposed by Health Canada), the tolerable daily intake is not exceeded for two methods of estimating daily intake of fluoride (i.e. it is not exceeded in column A or B of Table 2). Using the estimate that maximizes the amount of water consumed per day (i.e. column C of Table 2), the tolerable daily intake is exceeded for children less than 5 years of age. However, even if the tolerable daily intake is exceeded for children, Health Canada notes that the rates of severe and moderate dental fluorosis in Canada are very low, which may indicate that the tolerable daily intake set by Health Canada is overly conservative[17].

Table 2: Total estimated chronic inorganic fluoride exposure from all sources (tap water, non-tap water (bottled water), food, toothpaste and air) in mg/kg/day assuming water is fluoridated at 1.0 mg/L and no fluoride supplements

Population Subgroups	A Assumes non-tap water is 0.5 mg/L; Assumes total daily water consumption based on a model[18]	B Assumes non-tap water is 1.0 mg/L; Assumes total daily water consumption based on a model[19]	C Assumes non-tap water is 1.0 mg/L; Assumes water consumption is 1 litre per day for a 10-kg child and 2 litres per day for 70-kg adult[20]
All infants (<1 year)	0.070	0.082	0.113
Nursing	0.030	0.034	0.109
Non-nursing	0.087	0.100	0.115
Children 1-2 years	0.066	0.070	0.139
Children 3-5 years	0.060	0.063	NA
Children 6-12 years	0.040	0.042	NA
Youth 13-19 years	0.028	0.030	NA
Adults 20-49 Years	0.031	0.034	0.043
Adults 50+ years	0.031	0.034	0.042
Females 13-49 years	0.031	0.033	0.042

KEY POINT
Tolerable daily intakes of fluoride are set to prevent severe and moderate dental fluorosis in children most at risk (ages 1 - 4 years). Although these levels of intake may be exceeded in children at 1.0 mg/L of fluoride in drinking water based on some estimates, they are less likely to be exceeded at 0.7 mg/L of fluoride in London's drinking water. Rates of severe and moderate fluorosis in Canada are very low indicating fluoride levels in drinking water in Canada are sufficiently protective.

B.3 Fluoride in bones

Bone ash is a white powdery substance that results from burning bone. As bone accumulates fluoride, the amount of fluoride in bone ash is presented as a measure of fluoride exposure. Normal values have ranged from 326-2,390 ppm[21].

B.4 Fluoride in other tissues

In the National Research Council report, measures of the range of fluoride in other body fluids and body parts such as urine, blood (plasma and serum), saliva, hair, plaque, toe nails, finger nails etc are provided[22].

C. UNDERSTANDING THE STUDIES

The National Research Council report reviews numerous studies of different types or designs. The studies involve looking at the impact of fluoride on animals and people. The outcomes of the studies include changes in the genetic material of cells, changes in hormones or chemicals in the body, changes in fluoride levels in various tissues or organs in the body and the development of disease states. There are strengths and weaknesses inherent in the design of these studies and additional strengths and weaknesses related to how well the studies were performed by the researchers.

When trying to draw conclusions from various studies, each study needs to be assessed individually with regard to design and quality. Then all of the studies need to be assessed in totality to determine the strength of the picture they are portraying. Conclusions are usually drawn by a group of experts looking at the totality of the evidence; these are called systematic reviews. Conclusions are easiest to draw when all studies have strong designs, are well performed and all of the studies find consistent results. Conclusions are hardest to draw when the studies are of weaker design, are executed poorly and/or the findings are inconsistent.

It is important to note that large effects are typically easy to determine. This means that if fluoride caused high rates of a disease or condition, this would be easy to find even using weaker study designs. In addition, when there is a large effect the results of different studies are more likely to be consistent. Sometimes large effects are obvious just by observation such as the effect of high levels of fluoride on dental fluorosis which was noted by practicing dentists in communities with very high levels of naturally-occurring fluoride. In contrast, small effects are much harder to find and require more studies with stronger designs that are well executed.

The following sections provide a general overview of the types of studies found in the National Research Council report. They are listed from the weakest design to the strongest design in terms of ability to reliably inform conclusions about human health impacts. A brief overview of the statistics used in these reports is also provided.

C.1 Genotoxicity studies and other in vitro studies

Genotoxicity studies look at the effects of fluoride on the genetic material of cells. The cells can be exposed to fluoride outside of the body (in vitro) or in the body (in vivo). The cells can be of animal or human origin. The effect of fluoride on animal cells of the parathyroid and pineal gland in vitro are also discussed in the National Research Council report.

C.2 Animal studies

These studies expose animals to fluoride and then look at fluoride levels in various tissues or organs in the body, and/or at the impact on biochemical substances, hormones, behaviours or disease states. Studies in animals often use high doses of fluoride. The higher doses may be used because the animal's body may handle the fluoride differently than the human body, or may be intended to compensate for the fact that the studies are often of shorter duration than human exposures. Animal studies provide more informative results if the disease state is similar in the animal and in humans, and if the substance of interest (e.g. fluoride) is handled similarly in the animal and human body. Animal studies can be useful to generate hypotheses to be further studied in humans but their results must be considered along with human studies which are more applicable to the impact on humans.

C.3 Human studies (epidemiologic studies)

Studies of humans are called epidemiologic studies. There is a hierarchy of design among human studies. The study designs reviewed in the National Research Council report are listed below from weakest to strongest design.

C.3 i) Ecologic studies: These studies compare disease rates and exposure rates at the community level, rather than the individual level. For example, an ecologic study compares the rates of cancer among several communities according to the community's level of fluoride in water. These studies are a weak design because the researchers cannot be certain if the people with the disease (e.g. the people with cancer) were actually exposed to the substance of interest (e.g. fluoride) and to what extent. Researchers can only know the average rates of exposure in the community. As well, there can be many differences between the communities being compared aside from their levels of fluoride in water. These factors are not always recognized and cannot always be controlled for in this type of ecologic study.

C.3 ii) Semi-ecologic studies: In these studies, a group of people with a disease (e.g. a type of cancer) is compared to a similar group of people without the disease (called controls) with regard to the exposure of interest (e.g. water fluoride levels). In a semi-ecologic design, the exposure of interest (e.g. fluoride) is not determined for each individual in the study based on interviews of each person, but rather based on the general fluoride level of the community where the individual lives.

C.3 iii) Case-control studies: These studies are similar to semi-ecologic studies, in that a group of people with a disease (called cases) are compared to a similar group of people without the disease (called controls) with regard to the exposure of interest. However, a case-control study is a stronger design than a semi-ecologic study because each individual in the study is interviewed and their individual level of exposure is determined (e.g. total fluoride intake for each individual from various sources). Other important factors that may lead to disease can also be determined in the interview with each individual so that these factors can be compared between the cases and controls.

Case-control studies are good for studying diseases that occur infrequently. One weakness of case-control studies is that people are often asked to remember what they did many years ago and this information may be remembered differently between cases and controls. It is also important to choose the controls carefully to ensure that they come from a population that is generally similar to the cases.

C.3 iv) Cohort studies: These types of studies involve looking at one specific population and then comparing the disease rates of a group of people within the larger population who were exposed to a substance (e.g. fluoride), to another group within the population without that type of exposure. Occupational studies can be a cohort design, where a group of workers exposed to fluoride are compared to a group of workers who are not exposed to fluoride. In cohort studies it is important to determine if other relevant risk factors (e.g. smoking, drinking) are similar between the two groups in order to attribute any difference in disease rates to the exposure of interest (e.g. fluoride). Workers in occupational settings are often exposed to levels of fluoride that are much higher than those found in drinking water.

C.3 v) Randomized control trials: These represent the strongest type of epidemiological study. This type of study involves taking a group of people and randomly assigning one part of the group to receive the intervention (e.g. fluoride) and the other part of the group to receive a placebo (something that looks like fluoride but has no biologic activity). The entire group is then followed forward in time to see if they develop the outcome of interest (e.g. prevention of cavities or fractures). It is very difficult to study water fluoridation using a randomized control design, however, there are some studies that assess the use of fluoride in the treatment of osteoporosis. The researchers randomly assign people with osteoporosis to receive daily fluoride pills or to receive a placebo. These people are then followed forward in time to determine the impact of fluoride on the bone and to determine if one group is more or less likely to develop fractures. The problem with these studies is that the daily amount of fluoride used was substantially higher than the amount of fluoride that would be consumed in fluoridated water.

IMPORTANT POINT
Large effects are easy to find in epidemiologic studies. Smaller effects are more difficult to determine.

C.4 Statistics

In the National Research Council report, the numbers often used to assess whether fluoride increases or decreases the risk of a disease is called “the relative risk (RR)”. The relative risk is the rate of the disease in those exposed to fluoride divided by the rate of the disease in those not exposed to fluoride.

$$\text{Relative risk (RR)} = \frac{\text{rate of disease in those exposed to fluoride}}{\text{rate of disease in those NOT exposed to fluoride}}$$

A result of “1.00” would therefore indicate no risk. A protective effect from fluoride would result in a number less than 1.00 and an increased risk would result in a number greater than 1.00. The further the number is away from 1.00 the greater the potential risk or benefit from fluoride. The results of the study are more convincing if the relative risk increases progressively with increasing levels of exposure to fluoride. This is called a “dose response” relationship. In some studies, the term “odds ratio (OR)” is used. It works the same way as the relative risk.

Confidence limits are often attached to the relative risk or odds ratio. These are two numbers, a lower limit and an upper limit. The 95% confidence limit means that there is a 95% chance that the true value of the relative risk or odds ratio falls somewhere between the two numbers in the confidence limit. If the confidence limit contains the value “1.00”, the result is deemed to be “not statistically significant”, meaning that any increased or decreased risk, as indicated by the relative risk or odds ratio, may not be related to fluoride but to chance alone. If the confidence limit does not include the value 1.00, the relative risk or odds ratio is deemed to be “statistically significant” and likely to be due fluoride and not just to chance.

Sometimes, instead of a confidence limit, the statistic associated with the relative risk or odds ratio is a “p-value”. A p-value greater than 0.05 ($p>0.05$) means that the relative risk or odds ratio results are ‘not statistically significant”, meaning that any increased or decreased risk, as indicated by the relative risk or odds ratio, may not be related to fluoride but to chance alone. If the p-value is less than or equal to 0.05 ($p \leq 0.05$), the relative risk or odds ratio is deemed to be “statistically significant” and likely to be due fluoride and not just to chance.

D) FLUORIDE AND SPECIFIC BODY SYSTEMS

The following section of this document will provide a general overview of the findings of the National Research Council report for each body system. Context for interpreting the findings in relation to the fluoridation of London's drinking water is also provided.

D.1 Teeth[23]

General Findings

It should be noted that the National Research Council was asked to look at the adverse effects that might result from fluoride and not its beneficial effects in preventing tooth decay[24]. The report found that severe fluorosis (disruption of the surface of the enamel caused by fluoride) is extremely unlikely to occur at levels of fluoride in drinking water below 2.0 mg/L. This level of fluoride in drinking water will not completely prevent moderate fluorosis (brown discoloration of teeth) but will reduce the severity and occurrence to 15% or less of the population[25].

Context

A U.S. survey conducted between 1999 and 2004 found that 3.6% of 12-15 year olds had moderate or severe fluorosis, 8.6% had mild fluorosis, and 28.5% had very mild fluorosis[26]. Mild and very mild fluorosis are generally only noticeable by a dental health professional. By comparison, in Health Canada's Canadian Health Measures Survey conducted between 2007 and 2009, the investigators found no severe and almost no moderate fluorosis in children between 6 and 12 years of age. Mild and very mild fluorosis were identified in 4% and 12% of these children respectively[27].

Fluorosis rates are expected to be higher in the U.S. than in Canada because the U.S. range for adjusting the fluoride in drinking water is 0.7 to 1.2 mg/L, while in Canada it is lower, at 0.7 mg/L. There is a recommendation in the U.S. to move fluoridation levels to 0.7 mg/L as well. The acceptable levels for naturally-occurring fluoride in drinking water are also higher in the U.S. than in Canada (2 - 4 mg/L in the U.S. compared to 1.5 mg/L in Canada).

D.2 Musculoskeletal Effects[28] (Bone and Joints)

D.2 i) Fractures[29]

General Findings

Because fluoride accumulates in the bone, there has been a lot of attention given to its effect on bone. The National Research Council report outlines a variety of hypotheses with regard to how fluoride affects the bones, including its effects on osteoblasts (the

cells that make bone) and osteoclasts (the cells that break down bone). It is known that fluoride increases the density of bones and it was used in the past as a medication to treat osteoporosis in the hope of preventing fractures. Studies using high doses (20 to 34 mg/day) of fluoride to treat osteoporosis in humans have indicated that it may slightly decrease vertebral fractures (fractures of the spinal bones) and may increase the risk of non-vertebral fractures (e.g. hips, wrist etc.) after 4 years of use[30].

Five studies of fracture risk related to drinking water containing near 4 mg/L of fluoride were reviewed in the National Research Council report and indicated an increased risk of fractures[31]. The Committee concluded that "the weight of evidence supports the conclusion that lifetime exposure to fluoride at drinking water concentrations of 4 mg/L is likely to increase fracture rates in the population, compared with exposure to fluoride at 1 mg/L, particularly in some susceptible demographic groups that are prone to accumulating fluoride into their bones"[32].

When looking at fluoride concentrations around 2 mg/L, the National Research Council Committee assessed four studies and concluded that the "available epidemiologic data for assessing bone fracture risk in relation to fluoride exposure around 2 mg/L is suggestive but inadequate for drawing firm conclusions about the risk or safety of exposures at that concentration"[33]. The National Research Council report also commented on the review done by McDonough et al. at York University in the United Kingdom in 2000. This review of multiple fracture studies compared the fracture risk in fluoridated areas at approximately 1.0 mg/L to non-fluoridated areas and concluded that the studies were evenly distributed around the no effect mark, but that statistical testing showed significant heterogeneity among studies (meaning the variation in the results of the studies made it difficult to combine them to get a single estimate of the risk)[34].

Context

The McDonough et al. review done by York University is most relevant to fluoride in drinking water at the levels used in London (0.7 mg/L). It reviewed 29 studies that assessed the fracture risk of water fluoridated at levels closest to 1.0 mg/L compared to the lowest water fluoride level reported and concluded "The best available evidence on the association of water fluoridation and bone fractures (27 of 29 studies evidence level C – *Level C" means: lowest quality of evidence, high risk of bias*) show no association."[35] Similarly, a later review published by the Australian Government in 2007 concluded the following: "The authors of the three existing systematic review [sic] concur that water fluoridation at levels aimed at preventing dental caries has little effect on fracture risk – either protective or deleterious. The results of the subsequent original studies support this conclusion, although suggest that optimal fluoridation of 1 ppm may indeed result in a lower risk of facture when compared to excessively high levels (well beyond those experienced in Australia). One study also indicated that optimal fluoridation levels may also lower overall fracture risk when compared to no fluoridation (the latter was not the case when hip fractures were considered in isolation)."[36]

D.2 ii) Skeletal fluorosis[37]

General Findings

Previous recommendations regarding the Maximum Contaminant Level of 4 mg/L were intended to prevent severe skeletal fluorosis (clinical stage III), a condition where fluoride accumulates in the bone and results in crippling calcifications in the joints, ligaments and vertebral bodies. The National Research Council Committee agreed that clinical fluorosis stage II was also a significant health concern as it resulted in joint pain, arthritic symptoms, calcification of ligaments and changes in some types of bone (osteosclerosis). Stage III skeletal fluorosis appears to be rare in the United States. The Committee could not determine if stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L[38].

Context

Skeletal fluorosis should not be a risk from water that has adjusted fluoride levels. Health Canada estimates that potentially adverse effects associated with skeletal fluorosis are likely to be observed at fluoride intakes greater than approximately 0.20 mg/kg/day[39], which is almost 5 times the estimated daily intake for an adult in the U.S. when the water fluoridation level is 1 mg/L. Other studies suggested that an intake of at least 10 mg/day for more than 10 years is needed to produce clinical signs of the milder forms of skeletal fluorosis[40].

D.2 iii) Arthritis[41]

General Findings

Based on the small number of studies and their conflicting results, the National Research Council Committee determined that there is likely to be no effect of fluoride on arthritis at environmental doses[42].

D.3 Reproductive and developmental effects[43]

General Findings

This section of the National Research Council report looked at the impact of fluoride on reproductive effects, such as hormone levels and fertility, in both males and females. The findings in this section are based mostly on animal studies which, in general, exposed the animals to high doses of fluoride. The National Research Council Committee concluded that “High-quality studies in laboratory animals over a range of fluoride concentrations (0-250 mg/L in drinking water) indicate that adverse reproductive and developmental outcomes occur only at very high concentrations”[44]. There are few available human studies on reproductive effects of fluoride, some assessing high doses

of fluoride. The National Research Council Committee concluded that "Overall, the available studies of fluoride effects on human reproduction are few and have significant shortcomings in design and power, limiting inferences"[45].

Down's syndrome related to fluoride in drinking water has been assessed in several studies. Two early papers from the 1950s and 1960s[46] [47] suggested an association between elevated rates of Down's syndrome and high water fluoride concentrations, with one also suggesting an association in babies born to younger women. However, these studies had several problems with the way they were conducted. Four other studies concluded that there was generally no association between Down's Syndrome and fluoride, although one study suggested a possible association among births to younger women[48]. There were problems with the methods of some of these studies as well. Problems with the Down's syndrome studies included not being sure that all the cases of Down's syndrome had been included into the analyses and not always controlling for the age of the mothers, since Down's syndrome is known to occur more often in babies of older mothers.

A review of the literature conducted in 2001 stated that an association between water fluoride concentrations and Down's syndrome was inconclusive[49]. Overall, the National Research Council report concluded that "studies of fluoride's effects on human development are few and have some significant shortcomings in design and power, limiting their impact"[50]. The reports also states "A few studies of human populations have suggested that fluoride might be associated with alterations in reproductive hormones, fertility, and Down's syndrome, but their design limitations make them of little value for risk evaluation." [51]

Context

The review of Down's syndrome and fluoride conducted in 2001 summarized six studies, five conducted in the US and one from England comparing Down's syndrome rates in fluoridated and non-fluoridated areas. The authors of the review noted that "This systematic review suggests that the evidence for an association between water fluoride level and the incidence of Down's syndrome is weak, and that all the identified studies were of poor quality" [52]. Studies looking at high dose fluoride exposure and Down's syndrome do not appear to have been conducted.

D.4 Neurotoxicity and neurobehavioral effects[53]

General Findings

The National Research Council report reviews three studies that compared the results of intelligence quotients (IQ) testing in pairs of Chinese villages - one with high and the other with lower levels of fluoride in drinking water. As well, one study compared two villages, one with high fluoride levels (as indicated by high levels of moderate to severe dental fluorosis) due to inhaling soot and smoke from domestic coal fires and the other

village with low or no dental fluorosis. These four studies found lower IQs in the villages with higher fluoride exposures. The National Research Council report states that "The significance of these Chinese studies is uncertain. Most of the papers were brief reports and omitted important procedural details"[54] The Committee did indicate that the consistency of the studies' results warranted further study.

A series of rat studies using a method of photographing fluoride and non-fluoride exposed rats in a small box indicated abnormal behaviour only in the rats exposed to the higher levels of fluoride. The National Research Council report noted "The results from these three experiments are difficult to interpret. One difficulty is interpreting the computer-derived categorization of activity patterns compared with behavioural descriptions commonly used by most animal researchers"[55]. A few other animal studies suggest changes in behaviour at very high doses of fluoride intake. The report also describes a few animal studies that compare the effect of aluminum fluoride with sodium fluoride and no fluoride on a small number of rats. The aluminum fluoride appeared to result in more pronounced effects on the rats, but abnormal outcomes and abnormal appearance of the brain were noted in both sets of exposed rats. The National Research Council report hypothesizes about an interaction between aluminum and fluoride in the brain and chemical changes in animal brains.

This chapter of the National Research Council report also discusses the potential impact of silicofluorides (e.g. hydrofluorosilicic acid, which is a type of silicofluoride that is added to the water in London in order to provide fluoride). The report discusses a potential increase in lead exposure or change in chemicals in the brain associated with silicofluorides. The report also quotes authors that concluded that "there is no "credible evidence" that water fluoridation has any quantifiable effect on the solubility, bioavailability or bioaccumulation of any form of lead"[56], arguing that the silicofluorides would be completely hydrolyzed (dissolved) before reaching the consumer's tap.

Context

Several studies have assessed IQ and fluoride levels, all from developing countries, most commonly China. Studies that compare the IQ levels in rural villages are problematic because it is difficult to know if the differences in IQ are true findings or if they are related to other unrecognized, unmeasured exposures. For example, IQ is known to be influenced by thyroid function and lead exposure. Based on the information in the National Research Council report, only one of the IQ studies in this chapter appears to have assessed iodine (which is related to thyroid function) and lead exposures between the villages being compared[57] [58].

Even if the findings were true, the average fluoride levels in drinking water in these studies were approximately three to five times higher than London's drinking water, and the applicability of findings in Chinese villages to cities in developed countries is unknown. No studies looking at IQ levels in developed countries related to fluoride exposure appear to have been conducted.

Health Canada's draft report stated "It *(the weight of the evidence)* does not support a link between fluoride exposure and intelligence quotients deficits, as there are significant concerns regarding the available studies, including quality, credibility, and methodological weaknesses"[59]. A fluoride review conducted by the European Commission wrote "SCHER *(Scientific Committee on Health and Environmental Risks)* agrees that there is not enough evidence to conclude that fluoride in drinking water may impair IQ"[60].

The studies of abnormal behaviour in rats exposed to high fluoride levels have also been questioned with regard to their methods. These studies only found effects on the behaviour of the animals at very high concentrations of fluoride and often failed to show effects on the animals at lower concentrations.

As hydrofluorosilicic acid dissolves completely in water, the public is never exposed to this compound and so any hypotheses about its potential effects on the brain are of limited relevance. Adding hydrofluorosilicic acid changes the acid balance in the water, and this is corrected by the water system operators so that the water is not any more corrosive or able to leach lead from the pipes than water without hydrofluorosilicic acid added.

D.5 Endocrine system[61]

General Findings

D.5 i) Thyroid[62]

The National Research Council report hypothesizes that fluoride may interfere with the formation of a thyroid hormone in the tissues in the body. Indirectly, this may result in enlargement of the thyroid gland (which is referred to as a goitre) and a deficiency state referred to as hypothyroid. Hypothyroid states are most commonly attributed to iodine deficiency, which is why iodine is added to salt to ensure sufficient ingestion. The National Research Council report also indicates that selenium deficiencies, which occur in China and Africa, can affect thyroid function[63].

The National Research Council report states that an association between fluoride and thyroid problems was suggested many years ago. In 1923, high rates of goitre were found in a town in Idaho which had high fluoride levels in their drinking water; children born after a switch to a low fluoride water supply "were not so affected"[64]. The report also quotes a study done in 1958 where fluoride was found to alleviate the symptoms of an overactive thyroid in 6 of 15 patients[65], suggesting fluoride may decrease thyroid function.

Several animal studies are quoted in the National Research Council report, some suggesting an association between fluoride and thyroid hormone levels consistent with the above hypothesis, some of which used high fluoride levels and some of which were also in animals that were iodine deficient. In humans, goitre has generally been

attributed to low iodine levels although some areas with goitres were not considered iodine deficient and may be associated with fluoride levels. The National Research Council report includes several human studies, most of which were conducted in developing countries. Some of the studies found no association between fluoride and thyroid function and/or goitre; some showed an association between fluoride and decreased thyroid function and/or goitre in areas with low iodine; and some studies, where iodine was considered adequate, found an association between high levels of fluoride and decreased thyroid function and/or goitre. No changes in thyroid function were noted in two studies of patients treated with higher doses of fluoride for osteoporosis[66].

It was noted in the National Research Council report that "Nutritional information (especially the adequacy of iodine and selenium intake) is lacking for many (iodine) and all (selenium) of the available studies on humans"[67]. It is also noted that "Many of the effects could be considered subclinical effects, meaning that they are not adverse health effects"[68]. The report concluded that adverse effects on health might be associated with seemingly mild changes in hormone concentrations therefore further research is needed to explore these possibilities.[69]

D.5 ii) Thyroid parafollicular cells[70]

The parafollicular cells of the thyroid produce a hormone called calcitonin. Calcitonin inhibits bone resorption (dissolving of bone by cells called osteoclasts). No animal studies measured calcitonin levels in relation to fluoride exposure. The few human studies involved people with skeletal fluorosis or workers exposed to high levels of fluoride and did find associations with increased calcitonin levels.

D.5 iii) Parathyroid glands[71]

Four small parathyroid glands are located at the back of the thyroid. They secrete a hormone called parathyroid hormone which controls the calcium levels in the blood. Animal studies, which generally use high levels of fluoride, suggest that fluoride increases the level of parathyroid hormone, particularly if there is also low calcium intake. Some studies in humans involving individuals receiving fluoride treatment for osteoporosis, having high occupational fluoride exposure or having endemic skeletal fluorosis suggested that fluoride may have an effect on calcium levels and/or parathyroid hormone levels. Various interactions between fluoride and the parathyroid glands are discussed.

D.5 iv) Pineal gland[72]

The pineal gland is a small organ located near the center of the brain. It produces a hormone called melatonin which is involved in the sleep-wake cycle and the onset of puberty and menopause. The pineal gland is calcified and because fluoride interacts with calcified tissues, the impact of fluoride on the pineal gland is of interest. The National Research Council report reviews one animal study and two human studies. The animal study used high doses of fluoride and found some effects on melatonin

production and sexual maturation. The two human studies compared the age of puberty for girls in fluoridated versus non-fluoridated or low fluoridated communities; the researchers generally found no significant difference between the two communities although one study suggests that the average age of onset of menstruation was earlier in a U.S. town with a fluoridated water supply compared to a town with an unfluoridated water supply[73].

D.5 v) Glucose intolerance[74]

Diabetes results from the body's inability to manage glucose. A small number of animal studies in diabetic and normal animals suggest that high doses of fluoride may impact the body's ability to handle glucose. Few human studies are presented, most involving populations with high exposures to fluoride. Some studies suggest an impaired tolerance of glucose and others do not.

Context

The endocrine chapter of the report appears to be one of the more complicated sections. Multiple endocrine organs are reviewed in considerable detail and several hypotheses are proposed. Animal studies generally involve high doses of fluoride and are not applicable to the low levels of fluoride in drinking water. The human studies also often used high levels of exposure such as doses once used to treat osteoporosis, doses in occupational exposures or exposures in areas with high levels of fluoride in the drinking water. The studies with high levels of fluoride in drinking water were often conducted in developing countries where there may be other nutritional factors that impact the results. The few human studies of the thyroid done in developed countries[75] [76] [77] do not show an impact on goitre (two studies) or thyroid function (one study).

The author(s) of this section of the National Research Council report attempt to calculate the levels of exposure in the subjects in the various studies (expressed as mg/kg/day) in a summary table[78]. These are, however, estimates only[79] and the report does not indicate in the summary table that many of the estimates are from people with evidence of high exposures to fluoride as manifested by skeletal fluorosis and/or severe enamel fluorosis. In addition, some of the estimates are based on very small numbers of subjects. The summary table also only highlights the studies that support an association and not the studies that indicate no association.

Very few studies were done to assess the impact of fluoride on thyroid parafollicular cells, the pineal gland or glucose intolerance and with the exception of studies of the pineal gland, most involved exposures to high levels of fluoride. For all the endocrine organs, the National Research Council report provides very little evidence to indicate that any effects would occur at the low levels used in adjusted drinking water. A recent review by the European Commission states that "A systematic evaluation of the human studies does not suggest a potential thyroid effect at realistic exposures to fluoride"[80]. A review of recent conventional sources of medical information reveals that fluoride exposure is not discussed as a cause of hypothyroidism or diabetes [81] [82] [83] [84] [85] [86] [87].

D.6 Gastrointestinal, renal, hepatic and immune system[88]

General Findings

D.6. i) Gastrointestinal[89]

A few case reports suggested that fluoridated water at 1.0 mg/L could result in gastrointestinal symptoms (nausea, vomiting, and abdominal pain) in some people. The National Research Council report suggests that these people may be particularly hypersensitive, although this was uncertain[90]. The report indicates that fluoride at 4 mg/L in the drinking water results in approximately 1% of the population experiencing gastrointestinal symptoms[91]. In areas of high levels of fluorosis, such as India, gastrointestinal symptoms are common, especially where there is poor nutrition. Animal studies that expose animals to levels that are generally between 100 and 1,000 times the blood fluoride levels that occur from drinking fluoridated water illustrate the effect that fluoride can have on the stomach lining and gastrointestinal tract[92]. The effect at 4 mg/L of fluoride in drinking water is not well studied, with most studies involving higher doses of exposure[93].

D.6 ii) Renal (kidneys) [94]

Fluoride is excreted via the kidneys so the kidneys may experience higher concentrations of fluoride than other organs of the body. A few studies have been conducted to explore the effect of fluoride on kidney stones and the findings were mixed, with the possibility of both increased and decreased rates of kidney stones suggested in association with fluoride[95].

There is evidence of temporary declines in kidney function after exposure to general anaesthetic agents which contain fluorine. Administration of these agents results in very high blood levels of fluoride (50 times higher than normal). It is uncertain if the effect on the kidney is due to the fluoride or other compounds that result from the metabolism of the general anaesthetic[96]. Studies of areas where fluorosis is endemic suggest high levels of fluoride may increase the risk of kidney problems in some people[97].The National Research Council report indicates that "There are no published studies that show that fluoride ingestion on a chronic basis at that concentration *(1.0 L per day of water with 1.0 mg/L of fluoride)* can affect the kidney." [98]

People with impaired kidney function or on dialysis can accumulate fluoride much more quickly than normal. Care must be used in the dialysis process to ensure proper functioning of the equipment to remove fluoride from water.[99]

D.6 iii) Hepatic system (liver) [100]

High doses of fluoride fed to animals can result in changes in the appearance of the liver. One study involving people exposed to high levels of fluoride for 18 months to treat osteoporosis found an increase in blood levels of liver enzymes but the concentrations were still in the normal range[101]. Available data were not deemed sufficient to draw conclusions about low-level, long-term fluoride exposures in humans[102].

D.6 iv) Immune system[103]

The bone marrow (inside of the bone) contains cells that differentiate into the cells of the immune system. In experiments on bone marrow cells outside of the body (in vitro), large doses of fluoride are required to affect the development of immune cells. Given that the amount of fluoride in the bone can be significantly higher than in other areas of the body, the National Research Council report indicates that it is theoretically possible that long term exposure to fluoride at high levels could result in levels in the bone that could affect the immune cells.[104] The effect on the immune system of fluoride from drinking water containing 4 mg/L has not been studied in humans and the effect of fluoride on people with immunodeficiencies has also not be assessed[105].

Context

Aside from a few case reports of people with gastrointestinal upset at 1.0 mg/L, the effects of fluoride on the gastrointestinal, kidney, liver and immune system appear to be related to high levels of fluoride exposure. However, the National Research Council report indicates that there are no human studies that carefully document the impact of 4 mg/L of fluoride on these systems[106]. The report concludes that "such effects are unlikely to be a risk for the average individual exposed to fluoride at 4 mg/L in drinking water. However, a potentially susceptible subpopulation comprises individuals with renal impairment who retain more fluoride than healthy people do"[107]. Given the effects on these systems are unlikely at 4 mg/L, they will be much less likely at lower levels such as the 0.7 mg/L used to fluoridate London's drinking water.

D.7 Genotoxicity and carcinogenicity[108]

General Findings

D.7 i) Genotoxicity[109]

Genotoxicity refers to the ability of a substance such as fluoride to produce effects on the genetic material of cells. The cells can be either of animal or human origin and can be exposed to the substance outside of the body (in vitro) or in the body (in vivo). Several of these tests are reported in the National Research Council report. The in vitro studies "are inconsistent and do not strongly indicate the presence or absence of

genotoxic potential of fluoride"[110]. Regarding the in vivo studies, the report states that "the inconsistencies in the results of these in vivo studies do not enable a straightforward evaluation of fluoride's practical genotoxic potential in humans." [111]

D.7 ii) Carcinogenicity[112]

One animal study found that male rats given very high doses of fluoride (100 - 175 mg/L) in their drinking water had a small increased risk of developing osteosarcoma (a rare cancer of the bone) compared to control rats. This effect was not seen in two other studies involving rats exposed to fluoride, although a study in mice showed an increase in noncancerous bone tumours at very high fluoride doses.[113]

The weight of evidence from epidemiological studies of cancer in people done before 1993 did not indicate a cancer risk to humans from fluoride exposures[114]. More recent studies focused mainly on bone cancers because of the results of the animal studies, fluoride's known ability to concentrate in bone and its ability to cause cells in bone to divide. Some studies have compared cancer rates in fluoridated versus non-fluoridated communities (ecologic studies). A few of these studies suggested an association between fluoride and osteosarcoma in young males, while several other studies found no association[115].

Another study design looked at people with osteosarcoma and compared their past exposures to fluoride with a group of similar people without osteosarcoma (case-control studies). True case-control studies use individual interviews to determine past fluoride exposures which give a more precise understanding of the level of exposure, although some studies use the general fluoride level of where the person lives to estimate their fluoride exposures (semi-ecologic studies). Two of these studies (one case-control and one semi-ecologic study) generally did not indicate an association between fluoride exposure and osteosarcoma. A case-control study by Bassin et al., which was done for her PhD research at Harvard, found an association between osteosarcoma and fluoride levels in boys, based on the fluoride levels they were exposed to at younger ages when bones were growing. (The Bassin et al. study was subsequently published.[116]) The National Research Council report describes this study as having "important strengths and major deficits"[117]. A follow-up study from the same department at Harvard was expected to be published several years ago, but is not yet available.

The National Research Council report outlines a few other studies related to cancers of interest such as kidney, bladder, oral-pharyngeal and uterine[118], the results of which are generally inconclusive. Overall, the National Research Council report concluded with regard to the epidemiological studies in people that "the combined literature described above does not clearly indicate that fluoride either is or is not carcinogenic in humans"[119]. Weighing all the cancer information, the report concluded that "On the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro) the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed."[120]

Context

Other reviews of cancer data state the following:

- York University, United Kingdom, 2000: "There is no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers."[121] It should be noted that this review was based on 26 studies, although 18 were noted to be the lowest level of evidence with the most risk of bias. The review was published before the result of the Bassin et al. study was available.

- Health Canada, 2009: "According to the findings and recommendations from the Expert Panel Meeting on fluoride held recently in Canada (Health Canada, 2008), the weight of scientific evidence does not support a link between fluoride and cancer."[122]

- European Commission, 2010: "SCHER *(Scientific Committee on Health and Environmental Risks)* agrees that some epidemiologic studies seem to indicate a possible link between fluoride in drinking water and osteosarcoma, but the studies are equivocal. There is no evidence from animal studies to support the link, and thus fluoride cannot be classified as to its carcinogenicity."[123]

Osteosarcoma is a rare cancer that occurs at a rate of approximately 3 per million people in the United States[124]. It can affect children and adolescents less than 20 years of age, and is slightly more common in males than females. In Middlesex-London, there is approximately one case of bone and joint cancer (a larger category that includes osteosarcoma) per year in those less than 20 years of age in males and females combined[125]. If an association exists between fluoride and osteosarcoma, the inconsistencies in the results of the studies would indicate that the risk is small.

D.8 Summary of fluoride and specific body systems

The National Research Council report stated that "In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that the EPA's MCLG *(Environmental Protection Agency's Maximum Contaminant Level Goal)* of 4 mg/L should be lowered."[126] The Committee did not make any recommendations with regard to the secondary maximum contaminant level of 2 mg/L.[127]

Table 3 provides a brief overview of the general findings from the National Research Council report and the information provided in this document to add context.

Table 3: Overview based on the general findings of the National Research Council report and information provided to add context to the findings

Body System		Overview
Teeth		Severe fluorosis does not occur at fluoride levels less than 2 mg/L of fluoride in drinking water; Moderate fluorosis occurs in less than 15% of people at 2 mg/L of fluoride in drinking water; ***Context*** No severe and almost no moderate fluorosis were found in Canada. Mild and very mild fluorosis were found in 4% and 12% respectively of children 6-12 years of age.
Musculoskeletal (Bones and Joints)	**Fracture**	Lifetime exposure to fluoride at drinking water concentrations of 4 mg/L is likely to increase fracture rates in the population, compared with exposure to fluoride at 1 mg/L, particularly in some subgroups of people such as those with renal disease; Fracture risk at 2 mg/L of fluoride is suggestive but inadequate to draw conclusions; The totality of studies on fluoride in drinking water at approximately 1.0 mg/L indicates no effect on fractures.
	Skeletal fluorosis	Stage III skeletal fluorosis is rare in the United States. Stage II skeletal fluorosis is also a health concern but rates in the United States are unknown at 4 mg/L of fluoride in drinking water. ***Context*** Based on estimates of fluoride exposure levels likely to cause fluorosis, this outcome would be very unusual at low levels of fluoride in fluoridated drinking water.
	Arthritis	Likely to be no effect of fluoride on arthritis at environmental doses.
Reproductive and developmental (Down's syndrome)	**Reproductive**	Animal studies show reproductive and developmental effects only at very high levels of fluoride; The few studies done in humans have significant shortcomings in design and power, limiting inferences.
	Down's syndrome	The few Down's syndrome studies are of poor quality and the results are inconclusive making them of little value for risk evaluation.

Body System		Overview
Neurotoxicity and neurobehavioral (IQ)		Studies comparing villages in China found lower IQs in villages with higher fluoride levels; Animal studies found effects on the behaviour of animals at high levels of fluoride exposure; some of the studies used different methods than commonly used by researchers. ***Context*** IQ studies considered to have problems with how they were conducted; Studies of IQ in humans involved higher levels of fluoride exposure and have been conducted in developing countries where nutritional, educational, income and environmental factors differ from developed countries.
Endocrine (thyroid, thyroid parafollicular cells, parathyroid, pineal gland, glucose intolerance)	**Thyroid**	Some studies suggest that abnormal thyroid function and/or goitre may be associated with higher levels of fluoride, particularly when iodine levels are low. ***Context*** Studies suggesting an association between fluoride and thyroid were conducted in developing countries with other potential nutritional factors and environmental exposures that may influence the results.
	Parathyroid	High levels of fluoride may have an impact on calcium and/or parathyroid function.
	Thyroid parafollicular, pineal gland, glucose intolerance	Few studies presented.
Gastrointestinal, renal (kidney), hepatic (liver) and immune system	**Gastrointestinal**	Gastrointestinal effects can occur at high levels of fluoride.
	Kidney	Effects of fluoride on kidney stones mixed between promoting stones and protecting against stones. High levels of fluoride may cause adverse effects on the kidney. No studies show effects on the kidneys at low levels of fluoride.
	Liver	Available data insufficient to draw conclusions about low-level, long-term fluoride exposure.
	Immune system	The effect of 4 mg/L of fluoride in drinking water has not been studied in humans and the effect of fluoride on people with immunodeficiencies has also not been assessed.
Genotoxicity and carcinogenicity (cancer)	**Genotoxicity**	Inconsistent findings make evaluation difficult.
	Cancer	Cancer studies mainly focused on osteosarcoma; some studies have suggested an association between fluoride and osteosarcoma in young men while other studies have not.

E. CONCLUSIONS

The National Research Council report is intended to assess the safety of levels of naturally-occurring fluoride between 2 and 4 mg/L in drinking water in the United States. The report provides a review of both animal and human data related to possible effects of fluoride on many systems of the body with a focus on research conducted since1993.

Because the National Research Council report is intended to address the effects of fluoride at levels between 2 and 4 mg/L, it often does not allow conclusions to be drawn regarding lower levels of fluoride exposure. In general, the animal studies reviewed in the National Research Council report involved using doses of fluoride well above those that would be encountered in London and any findings at these levels of exposure likely have little applicability to London's drinking water. Many of the studies in humans also assess higher levels of fluoride exposure than would be experienced from London's drinking water. These studies include: people whose drinking water has high levels of naturally-occurring fluoride levels; people exposed to fluoride in air from cooking sources; workers exposed to fluoride occupationally; people who took high doses of fluoride as part of studies to assess its potential effects on treating osteoporosis, and people who were given fluorinated anaesthetic agents. It also should be noted that studies of high naturally-occurring levels of fluoride were often done in small communities in developing countries such as villages in China. Many factors differ between these developing countries and developed countries, including nutrition, other environmental exposures, education and income; therefore, studies from developing countries have questionable applicability to developed settings such as London.

Human research into possible causal mechanisms is pursued based on clinical observations, the understanding of biologic mechanisms and animal research. Considerable research has been done into the causes of cancer, diabetes and thyroid disease. Possible associations between cancer and fluoride have been studied in the past, however, low levels of fluoride exposure have not been identified as an area for major research in relation to diabetes or thyroid disease.

Large effects are generally easy to identify, therefore, if fluoride had a large impact on diseases such as osteosarcoma these effects should be easy to detect and replicate. Large effects may be apparent based on clinical observations alone. Even studies with poor designs and inherent weaknesses may find large effects. Smaller effects are more difficult to determine and require more studies with better designs and higher quality implementation. The National Research Council report identifies the need for additional research in several areas.

Years of widespread use of low levels of fluoride and the totality of the evidence of low-level exposures to fluoride do not indicate significant health concerns associated with its use. Careful attention to limiting exposure to fluoridated toothpaste when teeth are developing will help ensure no severe or moderate fluorosis and low rates of mild and very mild fluorosis, which are the only adverse effect proven to occur at low levels of fluoride exposure.

The final version of the Health Canada report on fluoride is expected shortly. It will assess the Maximum Acceptable Concentration (MAC) for fluoride in drinking water in Canada (1.5 mg/L) and will provide an additional systematic review of the effects of fluoride in drinking water.

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FLUORIDE IN DRINKING WATER

A SCIENTIFIC REVIEW OF EPA'S STANDARDS

Committee on Fluoride in Drinking Water

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Summary

Under the Safe Drinking Water Act, the U.S. Environmental Protection Agency (EPA) is required to establish exposure standards for contaminants in public drinking-water systems that might cause any adverse effects on human health. These standards include the maximum contaminant level goal (MCLG), the maximum contaminant level (MCL), and the secondary maximum contaminant level (SMCL). The MCLG is a health goal set at a concentration at which no adverse health effects are expected to occur and the margins of safety are judged "adequate." The MCL is the enforceable standard that is set as close to the MCLG as possible, taking into consideration other factors, such as treatment technology and costs. For some contaminants, EPA also establishes an SMCL, which is a guideline for managing drinking water for aesthetic, cosmetic, or technical effects.

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

In the early 1990s at the request of EPA, the National Research Council

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

COMMITTEE'S TASK

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

THE COMMITTEE'S EVALUATION

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

After reviewing the collective evidence, including studies conducted since the early 1990s, the committee concluded unanimously that the present MCLG of 4 mg/L for fluoride should be lowered. Exposure at the MCLG clearly puts children at risk of developing severe enamel fluorosis,

a condition that is associated with enamel loss and pitting. In addition, the majority of the committee concluded that the MCLG is not likely to be protective against bone fractures. The basis for these conclusions is expanded upon below.

Exposure to Fluoride

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

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

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

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

mg/kg/day for adults to 0.634 mg/kg/day for children. The corresponding intake range at 2 mg/L is 0.154 to 0.334 mg/kg/day for adults and children, respectively.

Dental Effects

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

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

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

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

two members concurred with the committee's conclusion that the MCLG should prevent the occurrence of this unwanted condition.

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

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

Musculoskeletal Effects

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

Skeletal Fluorosis

Skeletal fluorosis is a bone and joint condition associated with prolonged exposure to high concentrations of fluoride. Fluoride increases bone density and appears to exacerbate the growth of osteophytes present in the bone and joints, resulting in joint stiffness and pain. The condition is categorized into one of four stages: a preclinical stage and three clinical stages that increase in severity. The most severe stage (clinical stage III) historically has been referred to as the "crippling" stage. At stage II, mobility is not significantly

affected, but it is characterized by chronic joint pain, arthritic symptoms, slight calcification of ligaments, and osteosclerosis of the cancellous bones. Whether EPA's MCLG of 4 mg/L protects against these precursors to more serious mobility problems is unclear.

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

Bone Fractures

Several epidemiologic studies of fluoride and bone fractures have been published since the 1993 NRC review. The committee focused its review on observational studies of populations exposed to drinking water containing fluoride at 2 to 4 mg/L or greater and on clinical trials of fluoride (20-34 mg/day) as a treatment for osteoporosis. Several strong observational studies indicated an increased risk of bone fracture in populations exposed to fluoride at 4 mg/L, and the results of other studies were qualitatively consistent with that finding. The one study using serum fluoride concentrations found no appreciable relationship to fractures. Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to show an association might have been diminished in that study. A meta-analysis of randomized clinical trials reported an elevated risk of new nonvertebral fractures and a slightly decreased risk of vertebral

fractures after 4 years of fluoride treatment. An increased risk of bone fracture was found among a subset of the trials that the committee found most informative for assessing long-term exposure. Although the duration and concentrations of exposure to fluoride differed between the observational studies and the clinical trials, bone fluoride content was similar (6,200 to more than 11,000 mg/kg ash in observational studies and 5,400 to 12,000 mg/kg ash in clinical trials).

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

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

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

Reproductive and Developmental Effects

A large number of reproductive and developmental studies in animals have been conducted and published since the 1993 NRC report, and the

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

Neurotoxicity and Neurobehavioral Effects

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

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

Endocrine Effects

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

Effects on Other Organ Systems

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

Genotoxicity and Carcinogenicity

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

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

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

On the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro), the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and

mixed. Assessing whether fluoride constitutes a risk factor for osteosarcoma is complicated by the rarity of the disease and the difficulty of characterizing biologic dose because of the ubiquity of population exposure to fluoride and the difficulty of acquiring bone samples in nonaffected individuals.

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

DRINKING-WATER STANDARDS

Maximum-Contaminant-Level Goal

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

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

Secondary Maximum Contaminant Level

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

OTHER PUBLIC HEALTH ISSUES

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

RESEARCH NEEDS

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

- Exposure assessment

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

- Pharmacokinetic studies

— The concentrations of fluoride in human bone as a function of exposure concentration, exposure duration, age, sex, and health status should be studied. Such studies would be greatly aided by noninvasive means of measuring bone fluoride. Information is particularly needed on fluoride plasma and bone concentrations in people with small-to-moderate changes in renal function as well as in those with serious renal deficiency.

— Improved and readily available pharmacokinetic models should be developed. Additional cross-species pharmacokinetic comparisons would help to validate such models.

- Studies of enamel fluorosis

— Additional studies, including longitudinal studies, should be done in U.S. communities with water fluoride concentrations greater than 1 mg/L.

These studies should focus on moderate and severe enamel fluorosis in relation to caries and in relation to psychological, behavioral, and social effects among affected children, their parents, and affected children after they become adults.

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

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

- Bone studies

— A systematic study of clinical stage II and stage III skeletal fluorosis should be conducted to clarify the relationship between fluoride ingestion, fluoride concentration in bone, and clinical symptoms.

— More studies of communities with drinking water containing fluoride at 2 mg/L or more are needed to assess potential bone fracture risk at these higher concentrations. Quantitative measures of fracture, such as radiologic assessment of vertebral body collapse, should be used instead of self-reported fractures or hospital records. Moreover, if possible, bone fluoride concentrations should be measured in long-term residents.

- Other health effects

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