

Comments on

Fluoride in Drinking Water
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These comments are submitted to Health Canada in response to their September 2009 document for public comment entitled "Fluoride in Drinking Water." These comments are not to be considered a comprehensive review.

The author of these comments is a professional in the field of risk analysis, including exposure assessment, toxicity evaluation, and risk assessment. She has recently served on two subcommittees of the National Research Council's Committee on Toxicology, including the NRC's Committee on Fluoride in Drinking Water.

Goal of the assessment

p. 1, "The purpose of the consultation is to solicit comments on the proposed Maximum Acceptable Concentration on the approach used for the development of the guideline. . . . The purpose of the consultation is to solicit comments on the risk assessment conducted. . . ."

Health Canada's risk assessment for fluoride in drinking water should have two main goals: (1) to demonstrate from very high quality studies that fluoride in drinking water at the proposed Maximum Acceptable Concentration (MAC) will not harm any member of Canada's population; and (2) to demonstrate from very high quality studies that fluoride in drinking water at the recommended "optimal" concentration for dental health will, in fact, improve dental health. Both of these aspects should be demonstrated unequivocally before fluoride is deliberately added to drinking water supplies. Instead, Health Canada seems to think that unless there are very high quality studies demonstrating an adverse health effect, that such adverse health effects do not exist, and that fluoride at the "optimal" concentration is both safe and beneficial unless and until there are very high quality studies that demonstrate otherwise. This approach is exactly backwards for an organization whose responsibility is presumably to protect the health of its nation's population. By this rationale, the government (or the water authority) is dispensing medication to all its residents, regardless of individual benefit or even individual dose, and assuming that as long as no one looks for side effects of the medication, there will be none. The U.S. has long had this incentive to avoid good studies of possible adverse health effects of fluoride; Canada should not continue to follow suit.

Assessment approach

The purpose of a guideline such as the MAC should be to protect all persons, including members of susceptible population subgroups, from contaminant exposures that could cause them harm, with an adequate margin of safety. A risk assessment for chemical contaminants such as fluoride, therefore, should evaluate the contaminant intakes (mg/kg/day, i.e., mg of fluoride per kg body weight per day) associated with various adverse health effects and, if possible, identify an intake at or below which no one will experience any adverse health effect. When studies are less than ideal, it is necessary, in the interest of protecting health, to acknowledge the uncertainties and apply appropriate safety factors to ensure an adequate margin of safety. Some studies, for example, use sample sizes that are too small to be able to show a moderate effect; it is incorrect to assume that therefore there is no effect. Study populations are often grouped by

community, water source, or fluoride concentration in the water, rather than by individual intake. This results in study groups with overlapping intakes and makes it difficult to detect dose response relationships that do in fact exist.

Once a no-effect level or dose response relationship has been determined, it is then necessary to develop the guidelines or regulations necessary to keep the contaminant exposures of all members of the population below a level associated with adverse health effects. This requires special consideration of population subgroups who have higher exposures than usual or are more susceptible to adverse health effects from an exposure. For fluoride exposures, at-risk population subgroups include the very young, the very old, people with renal impairment (resulting in reduced fluoride excretion), and anyone who drinks large amounts of tap water or has high fluoride intake from some other source (NRC 2006a).

Among other things, Health Canada is not accounting for the range of tap water consumption, which probably varies over at least an order of magnitude for Canadian residents, as it does for U.S. residents, for a given age group (NRC 2006a). At Health Canada's recommended "optimal" concentration of fluoride in drinking water (0.7 mg/L), some bottle-fed infants will have fluoride intakes in excess of 0.17 mg/kg/day; some adults in the general population will have fluoride intakes in excess of 0.04 mg/kg/day, while individuals of any age with diabetes insipidus (DI) will easily have fluoride intakes of 0.11 mg/kg/day. At Health Canada's proposed MAC of 1.5 mg/L, some bottle-fed infants would have fluoride intakes in excess of 0.36 mg/L; some adults would exceed 0.09 mg/kg/day, while individuals with DI could have intakes of 0.23 mg/kg/day. Note that all these estimated intakes are for fluoride from tap water only, without contributions from other sources (NRC 2006a).

A number of adverse health effects can be expected to occur in at least some individuals when estimated average intakes of fluoride are around 0.05 mg/kg/day or higher (NRC 2006a; 2009). For persons with iodine deficiency, intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006a). The NRC (2006a) did not specifically evaluate health risks over the whole range of fluoride intakes, but in several cases, the available information included exposures to fluoridated drinking water in the U.S. (0.7-1.2 mg/L), a range relevant to Health Canada's recommendations. Clearly, Health Canada's "optimal" fluoride concentration of 0.7 mg/L is not protective of health for infants or persons with DI; at best it is marginally protective for healthy adults with average water intakes and no sources of fluoride exposure other than tap water.

"Optimal" concentration of fluoride in drinking water

The whole question of an "optimal" concentration assumes some dental health benefit. The University of York carried out perhaps the most thorough review to date of human studies on effects of fluoridation. Their work (McDonagh et al. 2000) is widely cited as showing the safety and efficacy of water fluoridation, but it actually does neither (Wilson and Sheldon 2006; Cheng et al. 2007). The report mentions a surprising lack of high quality studies demonstrating benefits, and also finds little evidence that water fluoridation reduces socioeconomic disparities:

Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken. (McDonagh et al. 2000)

Water fluoridation aims to reduce social inequalities in dental health, but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation. (Cheng et al. 2007)

Evidence relating to reducing inequalities in dental health was both scanty and unreliable. (Wilson and Sheldon 2006)

The apparent benefit is modest, about a 15% difference in the proportion of caries-free children (McDonagh et al. 2000). The American Dental Association (2005) states that “water fluoridation continues to be effective in reducing dental decay by 20-40%,” which would translate to < 1 decayed, missing, or filled permanent tooth (DMFT) in older children and adolescents (based on U.S. data from CDC 2005). Is this adequate justification for imposing inadequately characterized risks?

Most studies of benefits of fluoride intake or fluoridation have failed to account for a number of important variables, including individual fluoride intakes (as opposed to fluoride concentrations in the local water supplies), sugar intake, socioeconomic variables, and the general decline in caries rates over the last several decades, independent of water fluoridation status. Neither McDonagh et al. (2000) nor the ADA (2005) mention that fluoride exposure appears to delay the eruption of permanent teeth, although this has been known since the 1940s (Short 1944; NRC 2006a). A delay in tooth eruption alters the curve of caries rates with respect to age and complicates the analysis of age-specific caries rates (Psoter et al. 2005; Alvarez 1995; Alvarez and Navia 1989). Komárek et al. (2005) have calculated that the delay in tooth eruption due to fluoride intake may explain the apparent reduction in caries rates observed when comparisons are made at a given age, as is usually done.

Two recent papers, whose authors include members of Health Canada's expert panel, clearly show no dental health benefit from ingested fluoride. In particular, the single study that has examined caries experience in relation to individual fluoride intakes at various ages during childhood (the Iowa study) has found no association between fluoride intake and caries experience; caries rates (% of children with or without caries) at ages 5 and 9 were similar for all levels of fluoride intake (Warren et al. 2009). The authors state that “the benefits of fluoride are mostly topical” and that their “findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*” (emphasis in the original). Most of the children with caries had “relatively few decayed or filled surfaces” (Warren et al. 2009). The authors' main conclusion:

Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, firmly recommending an “optimal” fluoride intake is problematic. (Warren et al. 2009).

The second paper describes a national data set collected in the U.S. in 1986-1987 (more than 16,000 children, ages 7-17, with a history of a single continuous residence). No difference in caries rates in the permanent teeth of children is seen with different water fluoride levels (Table 1; Fig. 1; data obtained from Iida and Kumar 2009).

Table 1. Caries prevalence and fluorosis prevalence with water fluoride concentration.^a

Water fluoride concentration mg/L	Children with caries %	Children with fluorosis ^b %
< 0.3	55.5	14.6
0.3-0.7	54.6	19.6
0.7-1.2	54.4	25.2
> 1.2	56.4	40.5

^a Data for permanent teeth of children ages 7-17, calculated from data provided in Table 1 of Iida and Kumar (2009).

^b Includes very mild, mild, moderate, and severe fluorosis, but not “questionable.”

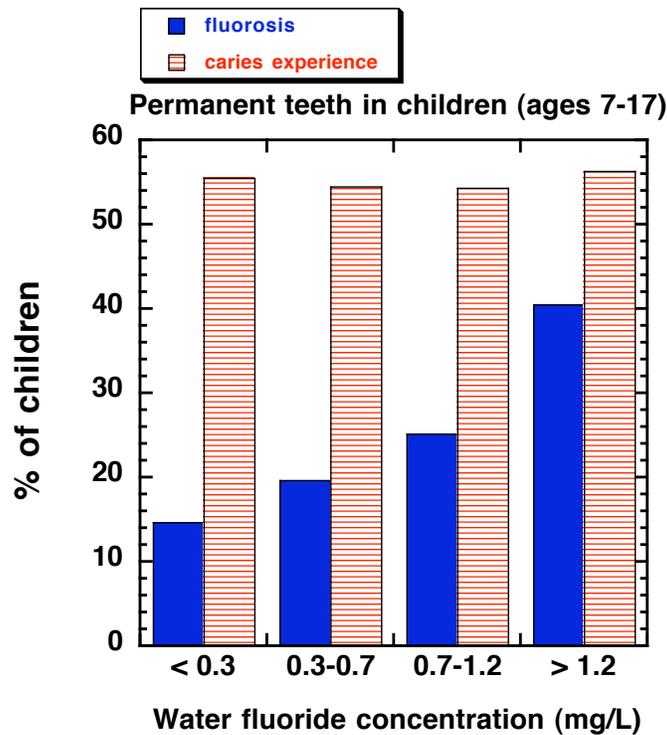


Fig. 1. Fluorosis prevalence and caries prevalence with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or caries experience. Numerical values are provided in Table 1 of these comments (above) and were calculated from data provided in Table 1 of Iida and Kumar (2009).

Maximum Acceptable Concentration

Health Canada proposes a maximum acceptable concentration (MAC) for fluoride in drinking water of 1.5 mg/L. The MAC is declared to be “protective of health, provided care is taken to follow Health Canada’s recommendations regarding other sources of exposure to fluoride” (p. 3).

Who is expected to take care to follow Health Canada’s recommendations? Members of the public? Are they adequately informed that if they fail to spit out their toothpaste, any adverse health effects from the local drinking water are their own responsibility? Do the local water authorities monitor their populations for “excess” consumption of toothpaste or tea? If “excess” consumption occurs, are the violators warned to reduce their fluoride intakes, or will the local water authorities reduce the water fluoride concentration to protect the health of their constituents?

The U.S. National Research Council (NRC 2006a) concluded that 4 mg/L is an unsafe concentration of fluoride in drinking water and is not protective of human health. The NRC did not attempt to identify a “safe” concentration, which obviously would be somewhere below 4 mg/L, if one exists. Health Canada now tries to say that 1.5 mg/L is safe for everybody, as long as they follow Health Canada’s recommendations, and that 0.7 mg/L is “optimal” and “well below” the MAC. Health Canada’s 1.5 mg/L is less than a factor of 3 below the NRC’s “unsafe” level of 4 mg/L. Health Canada’s “optimal” concentration is only a factor of 2 below the MAC. Yet the drinking water consumption probably varies by at least a factor of 10 for any given age group, apart from other sources of fluoride intake such as toothpaste. At best, Health Canada’s approach leaves no margin of safety and does not account for the full range of individual exposures in the population. However, as described above, a fluoride concentration of 0.7 mg/L, let alone 1.5 mg/L, will not protect all members of the population from adverse health effects; individual exposures for at least some persons will exceed levels at which adverse health effects can be expected to occur.

Additional comments

(1) p. 2, section 2.1, last paragraph on the page

As mentioned above, there is sufficient evidence to support a precautionary approach of limiting fluoride exposure (see also Tickner and Coffin 2006). To wait until there is absolute proof of adverse health effects due to fluoride exposure is to continue to provide an incentive not to do good studies. Instead, Health Canada should take the responsible approach, which is to require a high level of evidence that there are no adverse health effects before permitting, let alone encouraging, widespread and unmonitored exposure of entire populations, including many individuals belonging to high-risk subgroups.

(2) p. 3, section 2.4

A recommended “optimal” concentration of 0.7 mg/L cannot be considered “well below” the proposed MAC of 1.5 mg/L. A factor of 2 is not an adequate margin of safety when intakes vary by more than a factor of 10.

(3) p. 5, first paragraph (before section 5.0)

It should be pointed out that while fluoride has been used experimentally in the treatment of osteoporosis, it has not been approved for that use in the U.S. (Raisz et al. 2002), and its experimental use has often been accompanied by an increase in bone fractures rather than the desired decrease (NRC 2006a).

(4) p. 8, section 5.3, paragraph 3

These estimated fluoride intakes from fluoridated toothpaste are approaching a level at which adverse health effects can be expected to occur in some individuals (and for children with iodine deficiency, they reach or exceed that level), as described above. These are estimated average intakes only from toothpaste. The high intakes from toothpaste mentioned later in this paragraph would be expected to be associated with adverse health effects in some individuals. Why does Health Canada think it is safe to add additional fluoride intake from drinking water?

(5) p. 9, section 5.6, second paragraph

Given all the resources poured into fluoride research in the last several decades, it is an interesting admission that the best data were collected in the 1940s. See the comment above concerning the University of York study.

(6) p. 10, the bulleted items

Health Canada should inform its readers that the American Dental Association issued a brief statement to the effect that parents should not prepare infant formula with fluoridated water if they are concerned about the possibility of their child developing dental fluorosis (ADA 2006). The Iowa study indicates that high fluoride intake during the first 2 years of life is most important with respect to development of dental fluorosis of the permanent maxillary central incisors (the "top front teeth")--the teeth that most affect a person's appearance (Hong et al. 2006a).

(7) p. 24, section 9.1.1

There is no physiological requirement for fluorine or fluoride, and hence it cannot be considered an essential element. The Institute of Medicine's recommended Adequate Intake (AI) values are in the range at which adverse effects could be expected, and the Tolerable Upper Intake (TUI) values are in the range at which adverse effects would be likely, in at least some persons.

(8) p. 25, section 9.1.3, last paragraph

A much more extensive summary of bone fluoride concentrations, with discussion, is provided by the NRC (2006a).

(9) p. 25, section 9.1.3.1

There has been little or no effort in the U.S. to identify skeletal fluorosis of any stage. The possibility that a sizeable fraction of "bone and joint pain" in U.S. adults is attributable to fluoride exposure has not been addressed, although it is plausible given what is known about fluoride intakes.

(10) p. 27, section 9.1.3.3

The NRC (2006a) points out, but Health Canada does not, that the Texas studies compared the two towns after the high-fluoride town had been defluoridated for 18 months, time enough for reversal of some, perhaps many, effects.

(11) p. 28, section 9.1.3.4, part A

Regarding the Danielson et al. (1992) study, it should be pointed out that the authors reported a difference between women exposed to fluoride prior to menopause and those exposed afterwards. For women exposed prior to menopause, the fracture risk was considerably higher than for those not exposed to fluoride. Many studies of fracture risk have not looked at age-specific exposure, or have involved women exposed only after menopause, when fluoride uptake into bone is probably substantially lower.

(12) p. 29, part B, last sentence

Serum fluoride concentrations would give an indication of recent fluoride exposure, not necessarily of long-term exposure, while osteoporotic fractures would be a function of long-term fluoride exposure. Thus the exposure measure used by Sowers et al. (2005) is inappropriate for the study. In the ecological comparison (comparison of the two communities with different water fluoride concentrations), a higher incidence of bone fracture was seen in the community with higher water fluoride concentrations (NRC 2006a).

(13) p. 31, first full paragraph, discussion of the NRC's 2006 report

Health Canada gives an inaccurate characterization of the National Research Council's work. The NRC (2006a) did not restrict its attention to studies of fluoride in the range of 2-4 mg/L or above in drinking water. Many of the cancer studies and Down syndrome studies involved "fluoridated" water (0.7-1.2 mg/L). Many of the endocrine studies involved exposure ranges comparable to those expected for populations on fluoridated water. The discussions of exposure and of pharmacokinetics involved the whole exposure range, including fluoridated water. The committee directly addressed the question of whether 4 mg/L fluoride in drinking water is safe and concluded that it is not. The committee did not attempt to identify a "safe" concentration of fluoride in drinking water, meaning "a level at which no known or anticipated adverse effect on the health of persons occurs and which allows an adequate margin of safety" (definition of the Maximum Contaminant Level Goal, MCLG; USEPA 2006). As mentioned earlier, grouping of

study populations by water fluoride concentrations results in overlapping exposure groups and misclassification of exposures; studies ideally should classify participants by individual exposures rather than the concentration of fluoride in drinking water. Also, some studies used a fluoride concentration of 1 mg/L as a "control," which of course does not permit any conclusion about the "safety" of 1 mg/L of fluoride in the drinking water.

(14) p. 31, section 9.1.4

Health Canada should be aware that three U.S. courts have found fluoridated water to be carcinogenic to humans (described in detail by Graham and Morin 1999).

(15) pp. 32-33, discussion of Bassin's work

The case-control study by Bassin et al. (2006) is the only published study thus far to have looked at age-dependent exposure to fluoride. This study reported a significantly elevated risk of osteosarcoma in boys as a function of estimated age-specific fluoride intake. At the very least, this study indicates that similar studies of pediatric osteosarcoma that have not looked at age-dependent intake cannot be considered to show "no effect." Age- and sex-dependencies of cancer risk are biologically plausible and have been demonstrated for other types of carcinogenic exposures (e.g., radiation exposure; NRC 2006b). The contradictory results promised by Douglass and Joshipura (2006) have not been published to date, have not been peer-reviewed, and are not available for scientific examination or discussion; therefore, they can be given no weight in a responsible assessment. It is also important to note that the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans as reported by Bassin et al. (2006), and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas.

(16) pp. 33-34, NRC (2006) discussion of carcinogenicity of fluoride

The NRC (2006a) committee unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed." Referring to the animal studies, the committee also said that "the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans." The committee also discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk.

While the NRC committee did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the committee did not consider either "insufficient information" or "clearly not carcinogenic" to be applicable. The committee report (NRC 2006a) includes a discussion of how EPA establishes drinking water standards for known, probable, or possible carcinogens; such a discussion would not have been relevant had the committee not considered

fluoride to be carcinogenic. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances.

(17) pp. 34-35, discussion of male reproductive effects

Fluoride intake is likely to affect the male reproductive-hormone environment, beginning at intakes of around 0.05 mg/kg/day (NRC 2009). A "safe" intake with respect to male reproductive effects is probably below 0.03 mg/kg/day.

(18) p. 35, discussion of Down syndrome

The NRC (2006a) provides a thorough analysis of the Down syndrome data, including the difficulties associated with the Whiting review, which is the only one cited by Health Canada. The NRC discusses a possible mechanism for induction of Down syndrome and recommends further study.

(19) p. 38, discussion of "other health effects"

Health Canada fails to mention that the NRC (2006a) concluded that fluoride is an endocrine disruptor, and that exposure levels associated with endocrine effects are reached by people consuming fluoridated water, especially those with nutritional deficiencies.

Health Canada also fails to mention the adverse effects that are associated specifically with the use of silicofluorides as the fluoridating agent (NRC 2006a).

(20) p. 41, section 9.2.4, first paragraph

Health Canada fails to point out that animals require much higher exposures (5-20 times higher, or more; see NRC 2006a; 2009) than humans to achieve the same effects or similar fluoride concentrations in bone or serum. In other words, humans are considerably more sensitive than most animal species that have been studied.

(21) p. 46, re clastogenic or genotoxic effects of fluoride *in vitro*

A number of mammalian *in vitro* systems have shown dose-dependent cytogenetic or cell transformational effects from fluoride exposure (reviewed by NRC 2009). Depending on the experimental system investigated, *in vitro* genotoxic effects have been reported at fluoride concentrations at or above about 5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Bjørnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (0.07-0.09 mg/kg/day for an adult; NRC 2006a). Thus, kidney and bladder cells may potentially be exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*. In addition, cells in the vicinity of resorption sites

in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006a) and thus are also at risk for genotoxic effects. Human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

(22) p. 50, last paragraph

If there are very limited data supporting increased susceptibility to fluoride effects for certain groups of people, that reflects inadequate study of at-risk groups, not a lack of effects. It is irresponsible to assume that these people are adequately protected.

(23) p. 51, section 10.1 on dental fluorosis

Several papers reviewed by the NRC (2006a) have reported associations between dental fluorosis and increased risk of adverse health effects, including thyroid disease, lowered IQ, and bone fracture (Alarcón-Herrera et al. 2001; Zhao et al. 1996; Li et al. 1995; Lin et al. 1991; Desai et al. 1993; Yang et al. 1994; Jooste et al. 1999; Susheela et al. 2005). To the best of my knowledge, no studies in the U.S. or Canada have looked for associations between dental fluorosis and risk of other adverse effects. Once again, the failure to look for adverse health effects does not demonstrate the absence of adverse health effects.

In the Iowa study, the ranges of daily intake for children with and without fluorosis overlap considerably (Warren et al. 2009). For children in this cohort with intakes below 0.04 mg/kg/day for their first 3 years of life, fluorosis rates for both maxillary central incisors ranged from 12-18%; for intakes above 0.06 mg/kg/day, fluorosis rates were as high as 50% (Hong et al. 2006b). Eight individuals in the cohort were considered to have severe fluorosis (Hong et al. 2006b); their individual intakes were not reported, so one assumes that they did not necessarily have the highest intakes of the cohort. This is the same cohort for which Warren et al. (2009) reported no association between fluoride intake and caries status (discussed earlier). Levy et al. (2009) have reported weak relationships in this same cohort between fluoride intake during childhood and bone mineral concentration and bone mineral density as measured by dual-energy x-ray absorptiometry (DXA) at age 11, but so far they have not reported the dental fluorosis status in children with or without bone effects related to fluoride intake.

In the national data set collected in the U.S. in 1986-1987 (16,689 children, ages 7-17, with a history of a single continuous residence, discussed earlier), a clear dose response is seen for fluorosis in the permanent teeth of children with different water fluoride levels (Fig. 1; Table 1; data obtained from Iida and Kumar 2009). For water fluoride in the so-called "optimal" (for the U.S.) range of 0.7-1.2 mg/L, only 40% of children had no fluorosis, while 25% had definite fluorosis and the remaining 35% had "questionable" fluorosis.

(24) p. 56, discussion of the York review

McDonagh et al. (2000) found "little evidence that water fluoridation reduces socioeconomic disparities." To repeat:

Water fluoridation aims to reduce social inequalities in dental health, but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation. (Cheng et al. 2007)

Evidence relating to reducing inequalities in dental health was both scanty and unreliable. (Wilson and Sheldon 2006)

(25) p. 57, second paragraph

The U.S. still considers "optimal" to mean 0.7-1.2 mg/L, with 0.7 mg/L in the hottest states and 1.2 mg/L in the coldest states. It is interesting, therefore, to see Health Canada recommend 0.7 mg/L as "optimal," given Canada's temperature range compared to that of the U.S. While 0.7 mg/L is still too high for adequate protection of the population, the situation in the U.S. is clearly worse. As mentioned above, 0.7 mg/L is not "well below" 1.5 mg/L, when the range of total exposures for any given age group likely exceeds a factor of 10.

(26) p. 58, second full paragraph

Health Canada should mention that IARC's classification of fluoride with respect to carcinogenicity dates to 1982 and 1987 and obviously cannot have considered much of the currently available information.

(27) pp. 58-59

Health Canada is to be commended for considering moderate dental fluorosis to be an adverse effect. Canada is ahead of the U.S. in this regard. However, any fluorosis, even mild, indicates some combination of overexposure to fluoride during early childhood and individual susceptibility.

The data from the Iowa study (Hong et al. 2006a,b; Warren et al. 2009) probably constitute a much better set of data for obtaining a dose response for dental fluorosis than the data from the 1940s, especially since the Iowa study has evaluated age-specific individual fluoride intake from all sources. From these papers, it is clear that the intake ranges overlap considerably for children with and without fluorosis, but the higher the fluoride intake, the higher the likelihood of dental fluorosis.

(28) p. 60, next-to-last paragraph

Some of the papers from the Iowa study report the number of children with severe fluorosis (8 of 628; Hong et al. 2006b), but the individual fluoride intakes for those children are not given in the papers. These children may not have the highest exposures in the cohort.

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