Comments on

EPA's Fluoride Risk Assessment and

Relative Source Contribution

Documents

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These comments on recent reports from the U.S. Environmental Protection Agency's Office of Water (EPA 2010a,b) are submitted to the Environmental Protection Agency (EPA) in response to their January 7, 2011, announcements (EPA 2011a,b) and January 2011 fact sheet (EPA 2011c). These comments are not to be considered a comprehensive review of the EPA reports or of fluoride exposure or toxicity.

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 that dealt with fluoride exposure and toxicity, including the NRC's Committee on Fluoride in Drinking Water. She has also authored an Environmental Protection Agency report on fluoride toxicity.

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Summary

The comments below pertain primarily to EPA's recent reports on exposure and relative source contribution (EPA 2010a) and non-cancer risk assessment (EPA 2010b) for fluoride. The goal of these two reports is the derivation of a new Reference Dose (RfD) for fluoride. The RfD is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (EPA 2009). However, EPA's new RfD for fluoride is not protective for a number of adverse health effects. EPA inappropriately includes an estimate of benefit in its assessment of the risk of adverse effects; the assumed benefit is not supported by available data. The exposure estimate does not include some important subsets of the population. The uncertainty factor of 1 selected by EPA does not reflect limitations of the data used (EPA 2011d) and will not lead to protection of the U.S. population from deleterious effects. Thus, EPA's new Reference Dose for fluoride, 0.08 mg/kg/day, fails to meet the standards of a Reference Dose as defined by EPA.

(1) Evaluation of safety

EPA should be reminded of its definitions for the Maximum Contaminant Level Goal (MCLG) and the Reference Dose (RfD):

> **MCLG:** Maximum Contaminant Level Goal. A non-enforceable health goal which is set at a level at which no known or anticipated adverse effect on the health of persons occurs and which allows an adequate margin of safety. (EPA 2009)

> **RfD:** Reference Dose. An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. (EPA 2009)

> **Reference Dose (RfD):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments. (EPA 2011d)

EPA's recent risk assessment for fluoride (EPA 2010b) is based on protection of the population from severe dental fluorosis. Dental fluorosis, including severe dental fluorosis, is a well-known effect from overexposure to fluoride during the early years of life. The National Research Council (NRC 2006) concluded that severe dental fluorosis is an adverse health effect, not merely a cosmetic effect as EPA had previously determined for "objectionable" dental fluorosis (EPA 1989). It is certainly appropriate to protect the population from severe dental fluorosis. However, there are a number of other "known or anticipated adverse" or "deleterious" effects that should also be protected against. EPA's new RfD for fluoride of 0.08 mg/kg/day (EPA 2010b) is not adequately protective.

The NRC (2006) concluded that EPA's MCLG for fluoride (4 mg/L) was not protective, based on severe dental fluorosis, stage II skeletal fluorosis, and increased risk of bone fracture. These are adverse effects for which there is sufficient information in the literature to consider them to be "known." However, the NRC also described a number of other adverse health effects which can reasonably be "anticipated" from fluoride exposure, but for which the information base is much less complete. While the NRC did not need these additional adverse health effects or deleterious effects to conclude that the MCLG was inadequately protective, EPA should consider them in setting a new RfD or a new MCLG, in keeping with its definitions for the MCLG and the RfD.

A revised RfD and MCLG should continue to protect against "objectionable" dental fluorosis (defined as moderate or severe; EPA 1989), not just severe dental fluorosis. Raising the RfD to 0.08 mg/kg/day (EPA 2010b) from the previous value of 0.06 mg/kg/day (EPA 1989) will not be protective for "objectionable" dental fluorosis. Severe dental fluorosis is obviously an adverse health effect, given the increased risk for dental caries (NRC 2006; EPA 2010b); Health Canada (2009) considers moderate dental fluorosis to be an adverse effect, and the NRC (2006) reports the general consensus in the literature that both severe and moderate dental fluorosis should be prevented. The psychological and social ramifications of "objectionable" dental fluorosis are not well characterized, but it should be intuitive that "objectionable" dental fluorosis can be deleterious (causing harm or damage; New Oxford American Dictionary) to an individual's social or emotional well-being, whether or not EPA considers it to be an "adverse health effect." In addition, the cost to repair objectionable dental fluorosis can be considerable.

EPA has not considered the association of dental fluorosis with increased risk of other 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). For instance, data reported by Alarcón-Herrera et al. (2001) show a clear relationship between severity of dental fluorosis and increased likelihood of having had a bone fracture (Fig. 1). 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. However, the

failure to look for adverse health effects does not demonstrate the absence of adverse health effects. The available information indicates that an association between dental fluorosis and other adverse health effects can reasonably be "anticipated," supporting a need for EPA to protect against most or all dental fluorosis, not just severe dental fluorosis.

In addition to the "known" adverse health effects of dental fluorosis, skeletal fluorosis, and increased risk of bone fracture, "anticipated" adverse health effects from fluoride exposure or community water fluoridation include (but are not limited to) carcinogenicity, genotoxicity, endocrine effects, increased blood lead levels, and hypersensitivity (reduced tolerance) to fluoride. These effects (described in more detail below) are not as well studied as the dental and skeletal effects, which should indicate that a greater margin of safety is necessary to ensure protection of the population—"in the face of uncertain evidence it is important to act in a manner that protects public health" (Tickner and Coffin 2006). The incompleteness of the information base is not a justification to ignore these effects in setting a new RfD or MCLG. In addition, it should be noted that some of these effects may occur at lower fluoride exposures than those typically associated with dental or skeletal effects, such that protection against the dental or skeletal effects does not necessarily ensure protection against other anticipated adverse health effects.

A few comments regarding the interpretation of the available fluoride studies may be helpful. As Cheng et al. (2007) have described, a "negative" study may simply mean that the study was not sufficiently sensitive to demonstrate a moderate (as opposed to large) effect. This is often due to use of too small a sample size. In addition, study populations are often grouped by community, water source, or fluoride concentration in the water, rather than by individual intake. Due to the wide variation in drinking water intake, this approach results in study groups with overlapping intakes and makes it difficult to detect dose-response relationships that do in fact exist.

The few studies that have looked at age-dependent exposure to fluoride have found increased risks of adverse effects (e.g., Bassin et al. 2006 for osteosarcoma; Danielson et al. 1992 for hip fracture risk); studies that have not looked at age-dependent exposure cannot be assumed to provide evidence of no effect. Similarly, studies that have used a measure of current exposure where a cumulative measure would be more appropriate, or vice versa, cannot be assumed to demonstrate lack of an effect.

Studies of fluoride toxicity in laboratory animals are sometimes dismissed as irrelevant because the exposures or fluoride concentrations used were higher than those expected for humans drinking fluoridated tap water. It is important to know that animals require much higher exposures (5-20 times higher, or more; see NRC 2006; 2009) than humans to achieve the same effects or similar fluoride concentrations in bone or serum. In other words, humans are considerably more sensitive to fluoride than are most animal species that have been studied.

EPA based its new RfD only on severe dental fluorosis in part because adequate dose-response information was available for severe dental fluorosis but not for skeletal effects. While it would be nice to have good dose-response information for various adverse health effects, the lack of it should not be a justification to eliminate a "known" or "anticipated" effect from being considered in setting an RfD or MCLG. As described in the IRIS Glossary's definition (EPA 2011d), an RfD can be set from a NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level) in the absence of dose-response information.

In fact, 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 2006; 2009); in other words, a LOAEL for some adverse health effects is lower than EPA's new RfD, which is supposed to protect the population, including sensitive subgroups, from deleterious effects during a lifetime (EPA 2009; 2011d). For persons with iodine deficiency (one example of a sensitive subgroup), average intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006). The remainder of this section briefly summarizes some (not all) of the adverse health effects, known and anticipated, that should be considered in EPA's reevaluation of the drinking water standards for fluoride. Most of these effects have been reviewed in detail by the NRC (2006), although the NRC did not specifically evaluate health risks over the whole range of fluoride intakes or attempt to identify a "safe" level of fluoride exposure. Consideration of carcinogenicity and genotoxicity do not belong in a non-cancer risk assessment, of course, but they should be part of EPA's reevaluation of the drinking water standards and so are included here.

Skeletal fluorosis

Bone fluoride concentrations in the ranges reported for stage II and III skeletal fluorosis will be reached by long-term fluoride exposures of 0.05 mg/kg/day or higher (estimated from NRC 2006). Chachra et al. (2010) have recently reported bone fluoride content for residents of Toronto (fluoridated for 32-36 years at the time of the study) and Montreal (not fluoridated) who were undergoing total hip replacement surgery; most of the individuals had a diagnosis of osteoarthritis. Two of the 53 individuals in Toronto had bone fluoride concentrations in the range reported for skeletal fluorosis (NRC 2006), although both individuals would have been well into adulthood when exposure to fluoridated water began. The study did not include exposure histories; nevertheless, it does indicate that bone fluoride concentrations in fluoridated North American cities can be in the range reported for skeletal fluorosis.

Bone fluoride concentrations, radiologic changes, and symptoms are not clearly correlated (Franke et al. 1975). Most of the literature addresses high fluoride exposures over a few years; there has been essentially no investigation of effects of low exposures over many years and no effort to identify fluorosis of any stage in the U.S. "Arthritis" (defined as painful inflammation and stiffness of the joints) is the leading cause of disability in the U.S., currently affects at least 46 million adults in the U.S. (including 50% of the population > 65 years old), and is expected to affect 67 million adults in the U.S. by 2030 (CDC 2006). The possibility that a sizeable fraction of "bone and joint pain" or "arthritis" in U.S. adults is attributable to fluoride exposure has not been addressed, although it is plausible, given what is known about fluoride intakes.

Increased risk of bone fractures

The NRC (2006) concluded that lifetime exposure to fluoride at an estimated average daily intake of 0.08 mg/kg/day (average adult fluoride intake with water at 4 mg/L and equal to EPA's new RfD) is likely to result in higher bone fracture rates, and the available information suggests an increased likelihood of bone fracture for daily fluoride intakes of 0.05 mg/kg/day (average adult fluoride intake at 2 mg/L and equal to IOM's recommended intake). The Agency for Toxic Substances and Disease Registry (ATSDR) has identified a chronic-duration Minimal Risk Level

(MRL) for oral exposure to fluoride of 0.05 mg/kg/day, based on an increased risk of bone fracture (ATSDR 2003). The NRC's findings (NRC 2006) indicate that the ATSDR's MRL is not protective enough, and thus EPA's RfD is even less protective. The available studies consider fluoride intake only in terms of the concentration in the local drinking water, and most use fluoridated water (1 mg/L, corresponding to an average daily intake of 0.03 mg/kg/day for adults) as a control. Thus there is probably considerable overlap in exposures between groups, making effects more difficult to distinguish, and the entire dose response range of interest has not been well studied. The findings in humans are consistent with animal studies that have found increased brittleness of bones with increased fluoride exposure (Clark and Mann 1938; Turner et al. 1997; 2001).

Danielson et al. (1992) reported an increased relative risk for hip fracture in a fluoridated area of 1.27 (95% CI 1.08-1.46) for women and 1.41 (95% CI 1.00-1.81) for men. These 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. EPA (2010b, p. 85) includes the Danielson et al. study in a table of bone fracture studies but does not include the finding for men and does not discuss the issue of timing of fluoride exposure with respect to menopause.

The Iowa study reported effects on bone mineral concentration and bone mineral density with average childhood fluoride intakes of 0.02-0.05 mg/kg/day (Levy et al. 2009). Linear correlation between dental fluorosis and risk of bone fracture has been reported for children and adults (Alarcón-Herrera et al. 2001; Fig. 1). Bone fracture rates in children in the U.S. may be increasing (e.g., Khosla et al. 2003), but fluoride exposure has not been examined as a possible cause or contributor.

Carcinogenicity

Three U.S. courts have found water fluoridation to be injurious to human health, specifically that it may cause or contribute to the cause of cancer and genetic damage (described in detail by Graham and Morin 1999). The NRC's committee on fluoride toxicology unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed" (NRC 2006). 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 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 (see also Cheng et al. 2007).

While the NRC 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 2006) 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.

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. Osteosarcoma is a bone cancer that commonly results in amputation of an affected limb and may result in death. 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."

While a few other studies (e.g., Gelberg et al. 1995) have looked at individual fluoride exposure (as opposed to group or ecologic measures of exposure), these have looked at total fluoride exposure until time of diagnosis or treatment. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time") cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure.

The 1990 National Toxicology Program (NTP) study on sodium fluoride officially concluded that "there was *equivocal evidence of carcinogenic activity* of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals" (NTP 1990; italics in the original). According to the published report, a "small number of osteosarcomas occurred in mid- and high-dose male rats. These neoplasms occurred with a significant dose response trend, but at a rate within the upper range of incidences previously seen in control male rats in NTP studies" (NTP 1990). It is important to realize that the historic controls from previous studies had not had the special low-fluoride diet used for this study, and therefore more properly constitute a low- to mid-range exposed group rather than a control group. This and other concerns were described in a memo within the Environmental Protection Agency (Marcus 1990) and reported in the press (Hileman 1990). These concerns and the testimony before the U.S. Senate of the union representing EPA scientists (Hirzy 2000) should be taken seriously by the EPA.

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with a higher incidence in males than in females (Bassin et al. 2006). Sergi and Zwerschke (2008) indicate that 60-75% of cases are in patients between 15 and 25 years old. In the NTP 2-year study, fluoride exposure was begun when the animals were 6 weeks old, as is typical for NTP and similar studies (Hattis et al. 2004). Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the NTP study probably corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely, the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas. Therefore, this animal study cannot be interpreted as showing no evidence of

causation for pediatric osteosarcoma, although, properly interpreted, it does show evidence for causation of geriatric osteosarcoma.

Genotoxicity

Genotoxicity, or the ability to damage the genetic material (genes and chromosomes) of cells, is considered indicative of potential carcinogenicity. A number of mammalian *in vitro* systems have shown dose-dependent cytogenetic or cell transformational effects from fluoride exposure (reviewed by NRC 2009). Several reports suggest an indirect or promotional mechanism, e.g., inhibition of DNA synthesis or repair enzymes, rather than a direct mutagenic effect (Lasne et al. 1988; Aardema et al. 1989; Aardema and Tsutsui 1995; Meng and Zhang 1997). Human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

A recent paper by Zhang et al. (2009) describes a new testing system for potential carcinogens, based on induction of a DNA-damage response gene in a human cell line. Sodium fluoride tests positive in this system, as do a number of other known carcinogens, representing a variety of genotoxic and nongenotoxic carcinogenic mechanisms. Known noncarcinogens—chemicals not associated with carcinogenicity—did not test positive. The system described by Zhang et al. (2009) is considerably more sensitive than the older systems for most chemicals examined; a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006); for people with substantial fluoride intake, serum fluoride concentrations may also reach or exceed 0.5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine well in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen 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; based on NRC 2006), right at the intake expected with EPA's new RfD of 0.08 mg/kg/day. Thus, at EPA's RfD, kidney and bladder cells are probably exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*, especially when the more sensitive system of Zhang et al. (2009) is considered. Based on the results of Zhang et al. (2009), most tissues of the body are potentially at risk if serum fluoride concentrations reach or exceed 0.5 mg/L. 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 2006) and thus are also at risk for genotoxic effects.

Endocrine effects

The NRC (2006) concluded that fluoride is an endocrine disruptor. Endocrine effects include altered thyroid function or increased goiter prevalence (at fluoride intakes of 0.05-0.1 mg/kg/day, or 0.01-0.03 mg/kg/day with iodine deficiency), impaired glucose tolerance (at fluoride intakes above 0.07 mg/kg/day), a decrease in age at menarche in girls in fluoridated towns, and disruptions in calcium metabolism (calcitonin and parathyroid function, at fluoride intakes of

0.06-0.15 mg/kg/day or higher). ATSDR's toxicological profile for fluoride (ATSDR 2003) refers to an animal study of thyroid function that would give a lower MRL (value not given) than the MRL derived for bone fracture risk (0.05 mg/kg/day).

Thyroid dysfunction and Type II diabetes presently pose substantial health concerns in the U.S. (NRC 2006). Of particular concern is an inverse correlation between maternal subclinical hypothyroidism and the IQ of the offspring. In addition, maternal subclinical hypothyroidism has been proposed as a cause of or contributor to development of autism in the child (Román 2007; Sullivan 2009). Calcium deficiency induced or exacerbated by fluoride exposure may contribute to a variety of other health effects (NRC 2006).

Steingraber (2007) has described the decrease in age at puberty of U.S. girls and the associated increased risk of breast cancer and other problems. EPA (2010b, pp. 13, 87; 2010c, pp. 9-10) mentions that hormonal changes over recent decades, evidenced by earlier puberty (decreasing age of menarche) now in comparison with the 1940s, may affect the applicability of the study used to derive the RfD to today's population. EPA fails to consider the possibility that some of these hormonal changes may actually have been induced by fluoride exposure (reviewed by NRC 2006).

With respect specifically to thyroid effects, EPA should compare its approach for fluoride with that for perchlorate. EPA's recent press release on perchlorate (EPA 2011e) indicates that the regulation to be pursued for perchlorate is intended "to protect Americans from any potential health impacts." Perchlorate "may impact the normal function of the thyroid." "Thyroid hormones are critical to the normal development and growth of fetuses, infants and children." Perchlorate "may disrupt the thyroid's ability to produce hormones that are critical to developing fetuses and infants." As reviewed by NRC (2006), fluoride also "may impact the normal function of the thyroid" and "may disrupt the thyroid's ability to produce hormones that are critical to developing fetuses and infants." In addition, EPA (2011e) indicates that 5-17 million people may have perchlorate in their drinking water, due largely to unintentional contamination. In contrast, more than 184 million people, or more than 60% of the U.S. population (CDC 2009), have fluoride in their drinking water due to deliberate addition of the chemical.

Increased blood lead levels

An increased likelihood of elevated blood lead levels is associated with use of silicofluorides (usually H_2SiF_6 or Na_2SiF_6) as the fluoridating agent (NRC 2006; Coplan et al. 2007). Approximately 90% of people on fluoridated water in the U.S. are on systems using silicofluorides (NRC 2006). The chemistry and toxicology of these agents, especially at low pH (e.g., use of fluoridated water in beverages such as tea, soft drinks, or reconstituted fruit juices), have not been adequately studied (NRC 2006). Associations between silicofluoride use and biological effects in humans have been reported, in particular, elevated levels of blood lead in children and inhibition of acetylcholinesterase activity (reviewed by Coplan et al. 2007). A recent study in rats found significantly higher concentrations of lead in both blood and calcified tissues of animals exposed to both silicofluorides and lead (Sawan et al. 2010).

In addition to biological effects of silicofluorides, the interaction of silicofluorides (as the fluoridating agent) and disinfection agents (specifically, chloramines) increases the leaching of lead from plumbing fixtures into drinking water (Maas et al. 2005; 2007). A recent

Congressional investigation discussed the failure of the CDC to publicize information about high lead levels in drinking water and children's blood in Washington, D.C. (Leonnig 2010). The interaction of silicofluorides and chloramines is the probable explanation for the high lead levels (Maas et al. 2005; 2007). EPA considers lead to be a probable human carcinogen and to have no practical threshold with respect to neurotoxicity (EPA 2004b)—in other words, there is considered to be no safe level of lead exposure, and the MCLG for lead is zero (EPA 2009).

Additional adverse health effects

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

Grandjean and Landrigan (2006) list fluoride as an "emerging neurotoxic substance" that needs further in-depth studies. The major concern is neurotoxic effects during human development.

The NRC has reviewed the possible association between exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) and increased risk of Down syndrome (trisomy 21) in children of young mothers, discussed a possible mechanism, and recommended further study (NRC 2006). Fetuses with Down syndrome are less likely to survive to birth, due both to higher natural fetal loss and to a high rate of pregnancy termination (Buckley and Buckley 2008; Forrester and Merz 1999; Siffel et al. 2004; Biggio et al. 2004).

Hypersensitivity or reduced tolerance to fluoride has been reported for exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) or use of fluoride tablets (approximately 1 mg/day). Symptoms include skin irritation, gastrointestinal pain and symptoms (nausea, vomiting, diarrhea, constipation), urticaria, pruritus, stomatitis, chronic fatigue, joint pains, polydipsia, headaches, and other complaints (Waldbott 1956; 1958; Feltman and Kosel 1961; Grimbergen 1974; Petraborg 1977; Spittle 2008; reviewed by NRC 2006). Patients were often unaware that their drinking water contained fluoride. Symptoms improved with avoidance of fluoridated water and recurred with consumption of fluoridated water or with experimental challenge with sodium fluoride. Double-blind tests of patients have confirmed hypersensitivity to fluoride (Grimbergen 1974; Waldbott 1956; 1958). Many of the observed symptoms represent true allergic phenomena, while others (e.g., gastrointestinal symptoms) could be due to a lower level of tolerance for fluoride (intoxication at lower exposure; Waldbott 1956; 1958).

(2) Inclusion of benefit

The EPA has included an assumption of benefit in its risk assessment for fluoride, including the preservation of an intake of 0.05 mg/kg/day as desirable (based on IOM 1997) and exclusion of possible adverse health effects (in this case, with only severe dental fluorosis being considered) below an intake of 0.07 mg/kg/day (EPA 2010b). IOM (1997) based its recommended intake on an assumed cariostatic effect of ingested fluoride. A number of sources (reviewed by NRC 2006), including the CDC (2001), now indicate that any beneficial effect of fluoride on teeth is topical (e.g., from toothpaste), not from ingestion. Featherstone (2000) describes mechanisms by which topical fluoride has an anti-caries effect and states that "[f]luoride incorporated during tooth development [i.e., from ingested fluoride] is insufficient to play a significant role in caries

protection." "The fluoride incorporated developmentally—that is, systemically into the normal tooth mineral—is insufficient to have a measureable effect on acid solubility" (Featherstone 2000). "The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries" (CDC 2001). Fluoride concentrations in drinking water or saliva are too low to be contributing significantly to a topical anti-caries effect, especially since most drinking water is not "swished" around the teeth before being swallowed. CDC (2001) states that "The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low—approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas. This concentration of fluoride is not likely to affect cariogenic activity." Thus, as pointed out by one of the reviewers of EPA's recent risk assessment (EPA 2010c), it is not correct to treat fluoride as a "nutrient" with a recommended intake.

The same reviewer (EPA 2010c) also pointed out that a risk assessment for adverse health effects should be separated from any assessment of benefits or recommended intake. The reasonable approach would be to set an RfD and MCLG based solely on the risks of adverse health effects, with an adequate margin of safety (EPA 2009) or an uncertainty factor that adequately reflects limitations of the data used (EPA 2011d). Then if EPA is required to consider presumed benefits, that requirement can be taken into account, together with the health risks, in setting an enforceable level (i.e., the Maximum Contaminant Level). However, before compromising its mission of protecting the public from adverse health effects due to contaminants in drinking water, EPA should critically review the available data (described below), which do not support a benefit from fluoride in drinking water.

EPA no doubt is aware that the U.S. Food and Drug Administration (FDA) considers fluoride in toothpaste to be a non-prescription drug (e.g., FDA undated-a; undated-b) and fluoride "supplements" (usually tablets or lozenges) to be prescription drugs (e.g., Medline Plus 2008). The goal of community water fluoridation is to provide a dental health benefit to individuals and to the population generally (Federal Register 2010), as acknowledged by EPA's recent reference (Federal Register 2010) to a "treated population" and by the present effort to include a recommended intake in the risk assessment for fluoride (EPA 2010b). This in effect puts local governments and water treatment personnel in charge of administering a chemical (i.e., a drug) to the population in an effort to improve individual and population health (Cross and Carton 2003; Cheng et al. 2007). EPA's own exposure assessment (EPA 2010a) demonstrates that fluoride from tap water exceeds that from either non-prescription (toothpaste) or prescription (tablets or lozenges) fluoride sources, yet this exposure occurs without any monitoring for either efficacy or side effects, without the "drug information" or warning labels generally provided for drugs, and without any semblance of informed consent.

The University of York has carried out perhaps the most thorough review to date of human studies on effects of fluoridation. Their work (McDonagh et al. 2000) is often 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 less than 1 decayed, missing, or filled permanent tooth (DMFT) in older children and adolescents (based on U.S. data from CDC 2005).

Neither McDonagh et al. (2000) nor the ADA (2005) mentions that fluoride exposure appears to delay the eruption of permanent teeth, although this has been known since the 1940s (Short 1944; NRC 2006). 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—in other words, the apparent dental benefit from fluoride intake shown in some studies is simply an artifact of fluoride-induced delay in tooth eruption. EPA should not consider benefit of fluoride intake without properly accounting for delayed tooth eruption.

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. When World Health Organization data on oral health of children in various countries are compared, similar declines in caries over time are seen in all developed countries, regardless of fluoridation status (Cheng et al. 2007; Neurath 2005).

The only peer-reviewed paper to be published from California's major oral health survey in the 1990s reported no association between fluoridation status and risk of early childhood caries (Shiboski et al. 2003). The paper did not address other types of caries.

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 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) shows essentially no difference in caries rates in the permanent teeth of children with different water fluoride levels (Table 1; Fig. 2; data obtained from Heller et al. 1997; similar data can be obtained from Iida and Kumar 2009). Analysis in terms of mean DMFS (decayed, missing, or filled tooth surfaces) for the group (Fig. 3), as opposed to caries prevalence, shows an apparent 18% decrease between the low-fluoride (< 0.3 mg/L) and fluoridated (0.7-1.2 mg/L) groups. In absolute terms, this is a decrease of about one-half (0.55) of one tooth surface per child. One possible explanation is delayed tooth eruption, which was not considered in the study. Note that the mean DMFS for the highest fluoride group is higher than for either of the two intermediate groups, also indicating that DMFS scores are not solely a function of water fluoride concentration. The increased DMFS score with the highest water fluoride concentration suggests that the increased susceptibility of fluorosed teeth to caries eventually surpasses the apparent decrease in caries attributable to fluoride-induced delay in tooth eruption. When the data are examined by the distribution of DMFS scores (Fig. 4), no real difference in caries experience with respect to water fluoride concentration is observed. In contrast, the same data set shows a clear dose response for both fluorosis prevalence and fluorosis severity with fluoride concentration (Heller et al. 1997; Table 1; Fig. 5).

The available data, responsibly interpreted, indicate little or no beneficial effect of water fluoridation on oral health. EPA should not assume or suppose beneficial effects of community water fluoridation in evaluating the health risks from fluoride in drinking water.

(3) Estimation of exposure

EPA's exposure estimate (EPA 2010a) excludes children up to 6 months old. Given that dental fluorosis is associated with exposures during the first 6 months of life (Hong et al. 2006a,b), as well as later periods, these children should also be included in the exposure estimate. EPA's risk assessment document (EPA 2010b, p. 96) indicates that "mineralization of the secondary teeth begins at about 6 ± 2 months," which should be sufficient justification to include the youngest children in the exposure estimate. For other adverse health effects such as thyroid or neurological effects, infancy could be a critical exposure period. In addition, it is important to distinguish between breast-fed and bottle-fed infants, and between bottle-fed infants fed ready-to-feed formula and those fed formula prepared with tap water. These constitute readily identifiable subgroups; considering them in one group could lead to underestimates of exposure for infants fed formula prepared with tap water.

EPA's exposure estimate (EPA 2010a) does not include sensitive population subgroups, although these are to be protected in setting an RfD or MCLG (see definitions above). Groups known to be at risk of high fluoride intake include those with high water intake (e.g., outdoor workers, athletes, and individuals with diabetes insipidus or other medical conditions) or exposure to other sources of fluoride intake (NRC 2006). In addition, people with impaired renal function are at

higher risk of adverse effects per unit intake of fluoride, due to impaired excretion of fluoride and consequent higher fluoride concentrations in the body.

(4) Characterization of uncertainty

EPA (2010b, p. 105) has used an uncertainty factor of 1 in establishing its new oral RfD for fluoride, based on defining a level of intake "that provides anticaries protection without causing severe dental fluorosis." A value of 1 for the uncertainty factor is inappropriate for a number of reasons.

First, as described above, severe dental fluorosis is not the most sensitive or even the most deleterious adverse health effect reported for fluoride exposure, merely one for which a good dose-response curve can be generated and which leads to an RfD high enough to "protect" the alleged benefits of fluoride intake. EPA surmises, but cannot demonstrate, that the RfD will also be protective for skeletal effects and for severe dental fluorosis in primary teeth. As described above, available information for a number of other adverse health effects or deleterious effects indicates that an intake of 0.08 mg/kg/day will not be protective.

Second, it is inappropriate to consider possible benefits in deriving a level of intake that will be protective for adverse effects. For one thing, the benefits, if real, might not involve the same individuals as those at risk for the adverse effects. More importantly, as described above, the benefits at best are small and are probably an artifact of a fluoride-induced delay in tooth eruption. Any benefit from fluoride exposure is from topical exposure, not systemic ingestion.

Third, EPA (2010b, p. 106) claims that its toxicity database for fluoride is complete. Given that the same report describes weaknesses in the database for skeletal effects, how can the database be considered complete? In addition, EPA has not considered a number of other health effects considered plausible by NRC (2006), many of which would occur at lower exposures than those required for severe dental fluorosis. The database on these "anticipated" effects is incomplete, as evidenced by the number of recommendations for further research listed by the NRC (2006). Again, how can EPA consider its database to be complete?

Fourth, the exposure assessment does not include the youngest age group, although this age is probably important for several adverse health effects (including severe dental fluorosis) and can include some of the highest exposures (due to use of fluoridated tap water in preparation of formula).

Fifth, the risk assessment and exposure assessment do not include known population subgroups that could be more sensitive to the effects of fluoride or that could have high fluoride exposures. The data set used to derive the RfD does not include individuals living in hot areas and does include only whites (EPA 2010b). The Centers for Disease Control and Prevention (CDC) has reported that the black population in the U.S. has higher rates of dental fluorosis than whites, including higher rates of moderate and severe dental fluorosis (CDC 2005). EPA (2010b) describes at least two studies reporting higher dental fluorosis rates in blacks than in whites. How can an uncertainty factor of 1 provide adequate protection for the black population? What about other minority populations? Economically disadvantaged populations?

Sixth, the definition for the MCLG (given above) includes allowing for an adequate margin of safety. How can there be an adequate margin of safety when EPA assumes both a recommended

intake of 0.05 mg/kg/day and a lower limit of harm at 0.08 mg/kg/day (0.07 from water, 0.01 from other sources)? Where is the adequate margin of safety? This is especially important since drinking water intake can vary by more than a factor of 10, depending on age, activity level, and the presence of certain health conditions such as diabetes insipidus (NRC 2006; EPA 2004a).

Seventh, EPA is basing its risk assessment on a decades-old study of drinking water containing natural fluoride. Close to two-thirds of the U.S. population is supplied with drinking water artificially fluoridated with silicofluorides. As discussed above, there is still too much unknown about the chemistry of silicofluorides in plumbing systems and about the differences in physiological or toxicological effects in people depending on the type of fluoridation chemical used. Is EPA confident that a risk assessment based on natural fluoride in water is adequately protective for populations whose water is treated with silicofluorides?

EPA needs a serious reevaluation of its uncertainty factor, in order to provide adequate protection against "known and anticipated adverse health effects" to all members of the U.S. population.

(5) Other comments

EPA's fact sheet (EPA 2011c) is misleading when it says "The NRC report does not question the beneficial effects for fluoride at levels practiced for fluoridation programs." The NRC report (NRC 2006) actually says "Assessing the efficacy of fluoride in preventing dental caries is not covered in this report" (p. 14) and "As noted earlier, this report does not evaluate nor make judgments about the benefits, safety, or efficacy of artificial water fluoridation" (p. 16). While several (at least) individual committee members do question the benefits, safety, and efficacy of artificial water fluoridation, the committee as a whole did not address the issue, as it was not part of our charge. In fact, information in the NRC report indicates that some adverse health effects can reasonably be expected at exposure levels anticipated for people drinking artificially fluoridated water. The NRC report also brings up the largely unstudied hazards that are associated with use of silicofluorides for fluoridation of drinking water.

The descriptions of the stages of skeletal fluorosis (EPA 2010b, pp. 64, 70-71) are incorrect. These descriptions should correspond to the description on pp. 170-171 of NRC (2006), which was taken from p. 46 of a Public Health Service report (PHS 1991). EPA appears to have copied the description from the prepublication version of the NRC report (p. 139 of the prepublication version). The description was corrected in the final published version of the NRC report. EPA should be certain that it is referring throughout to the final version of the NRC report.

EPA should also be careful that it is accurately reporting what the NRC report has said. For example, in one place EPA (2010b, p. 72) refers to an individual with skeletal fluorosis as having "excessive" water intake, citing the NRC report. The NRC report, citing the original paper, simply says that water intake may have been "increased." "Increased" water consumption in a hot area simply means higher than expected for moderate climates; it could be totally appropriate for the hot climate and not at all excessive. In the peer review document for the risk assessment, EPA (2010c, p. 8) refers to NRC having identified a water fluoride level of 4 mg/L as being the potential threshold for skeletal effects. In fact, the NRC report said that a water fluoride level of 4 mg/L was not protective for skeletal effects and that 2 mg/L might not be either. The NRC

report did not examine the whole dose response range and did not identify a threshold for skeletal effects.

On pp. 18-19 of the peer review response document for the risk assessment (EPA 2010c), EPA indicates that they have nominated fluoride for future biomonitoring efforts at CDC. EPA should greatly encourage CDC to obtain this information, something which the NRC (2006) also recommended.

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

Water fluoride concentration	Children with no caries	Mean DMFS score [b]	Children with fluorosis [c]	Mean severity of fluorosis [d]
mg/L	%		%	
< 0.3	53.2	3.08	13.5	0.30
0.3 - < 0.7	57.1	2.71	21.7	0.43
0.7 - 1.2	55.2	2.53	29.9	0.58
> 1.2	52.5	2.80	41.4	0.80

[a] Data for permanent teeth of children ages 5-17 (caries experience and DMFS score) or 7-17 (dental fluorosis), with a history of a single residence, from Tables 2 and 5 of Heller et al. (1997).
[b] Decayed, missing, or filled tooth surfaces (permanent teeth).
[c] Includes very mild, mild, moderate, and severe fluorosis, but not "questionable."
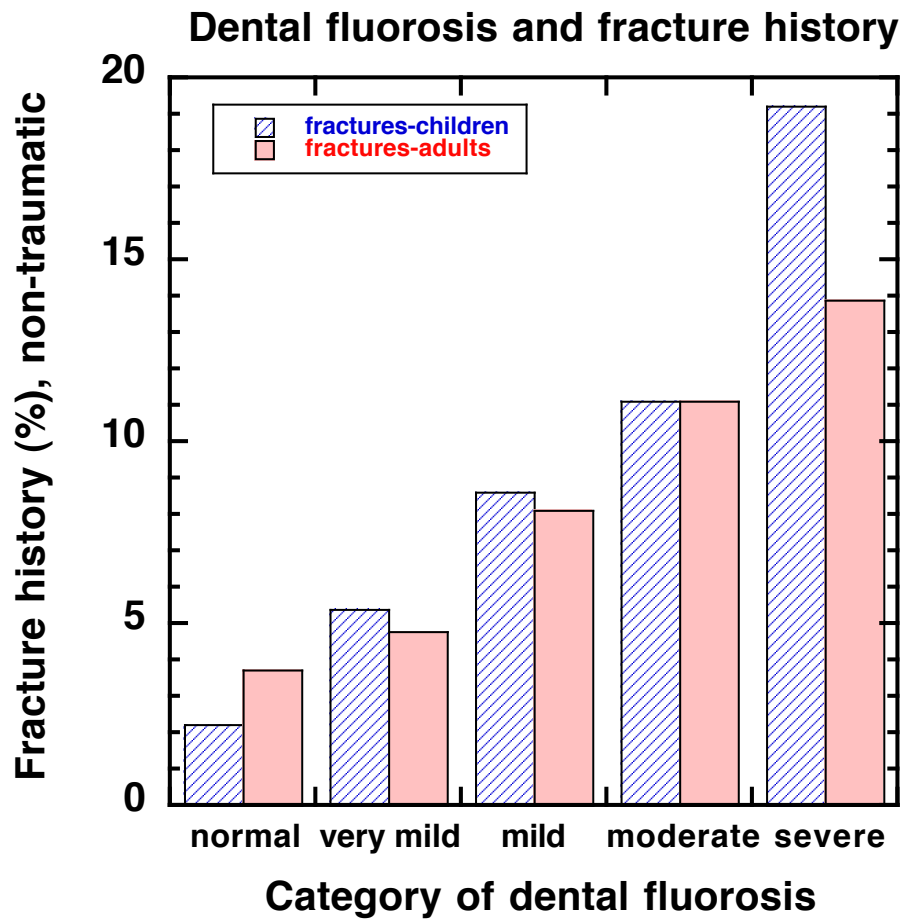[d] Dean's Community Fluorosis Index.

Fig. 1. Fracture history with category of dental fluorosis for children (ages 6-12) and adults (ages 13-60). Numerical values were obtained from information in Tables 5 and 6 of Alarcón-Herrera et al. (2001).
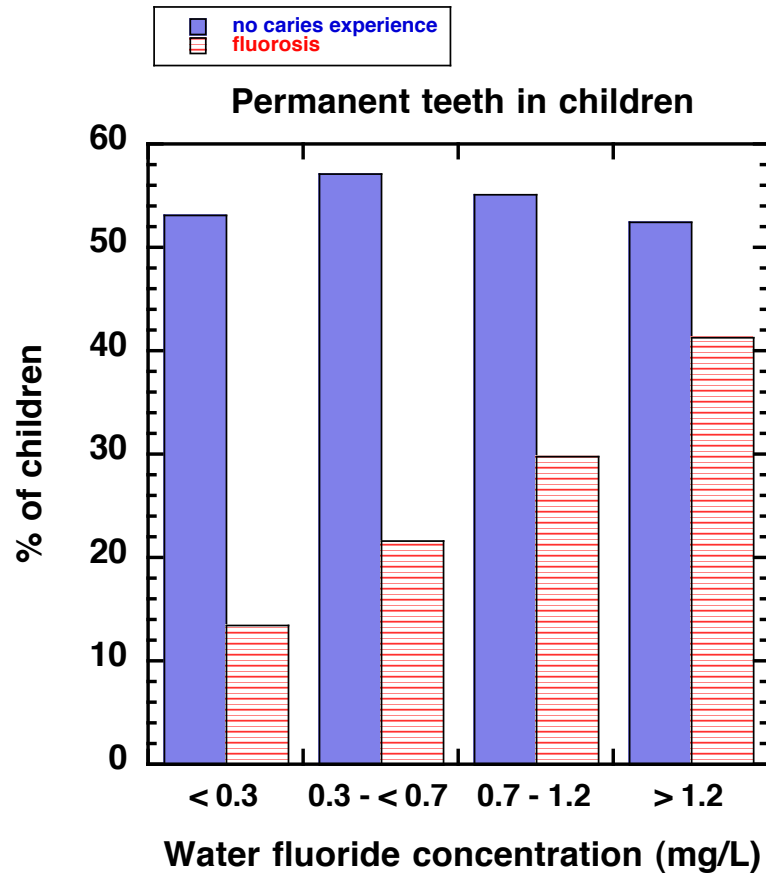
Fig. 2. Percent of children with no caries experience in the permanent teeth (DMFS = 0) and with fluorosis, with respect to water fluoride concentration. Data are shown as % of total children having no caries experience or having fluorosis (very mild, mild, moderate, or severe, but not questionable). Numerical values are provided in Table 1 of these comments and were obtained from Tables 2 and 5 of Heller et al. (1997).

Permanent teeth in children
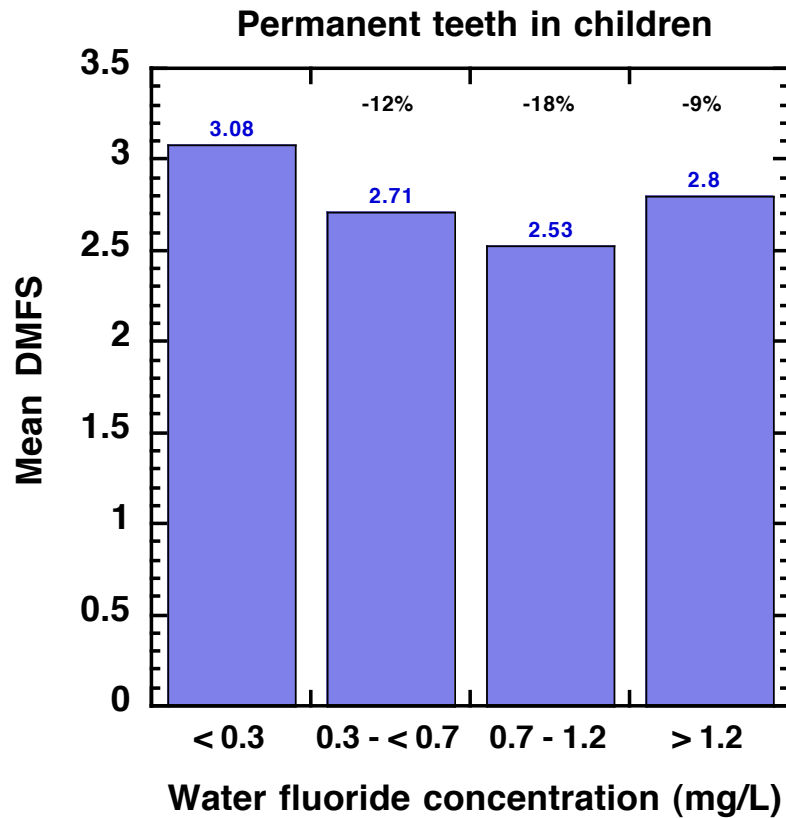
Fig. 3. Mean DMFS score (decayed, missing, or filled tooth surfaces in permanent teeth), with respect to water fluoride concentration. Numerical values are provided in Table 1 of these comments and were obtained from Table 2 of Heller et al. (1997). The percent difference with respect to the lowest fluoride group is also provided.
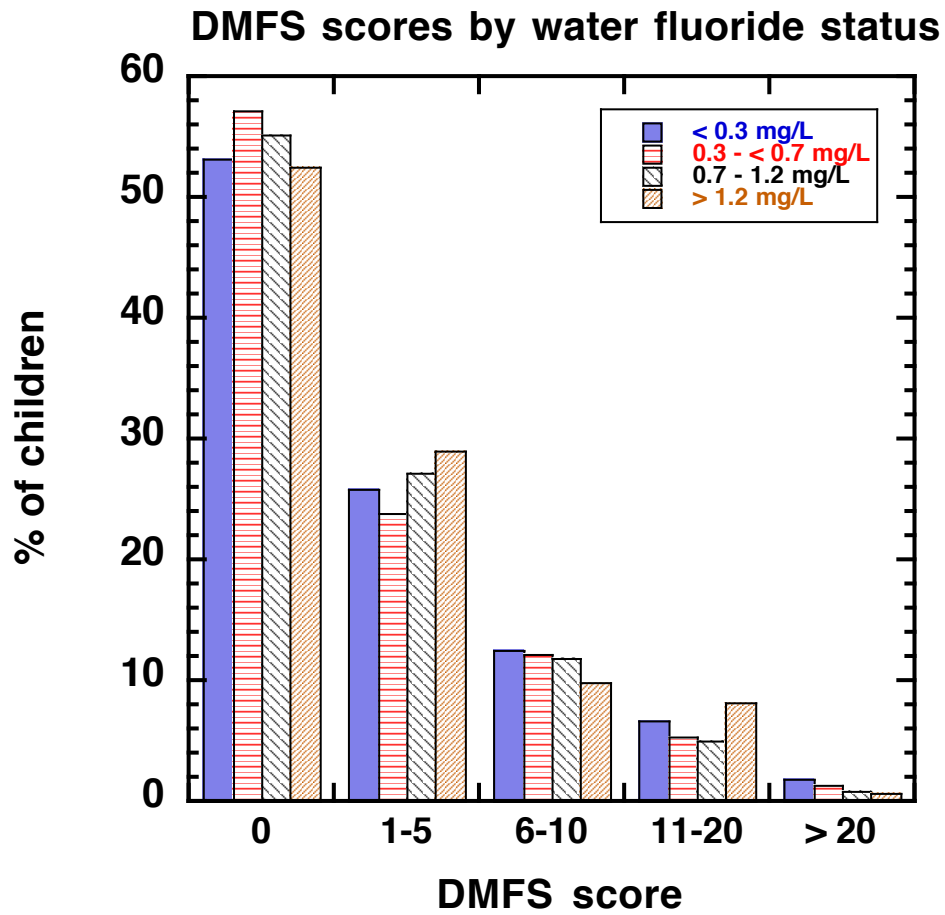
Fig. 4. Percent of children by DMFS score, with respect to water fluoride concentration. Data are shown as % of total children in a given group according to the number of decayed, missing, or filled tooth surfaces in the permanent teeth (DMFS). Data were obtained from Table 2 of Heller et al. (1997).
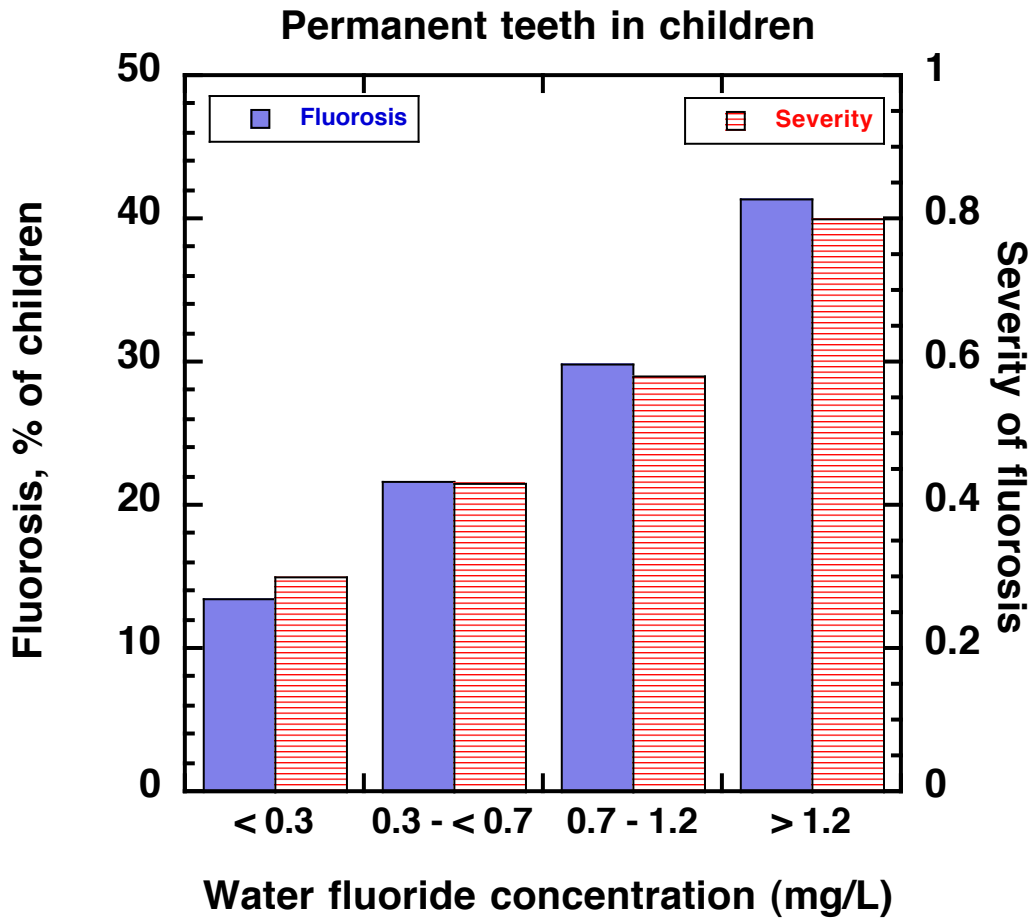
Fig. 5. Fluorosis prevalence and severity with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as (left) % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or (right) severity of fluorosis by Dean's Community Fluorosis Index. Numerical values are provided in Table 1 of these comments and were obtained from Table 5 of Heller et al. (1997).

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