Comments on
the Need for Revision of
the NPDWR for Fluoride

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These comments on the need for revision of the National Primary Drinking Water Regulations (NPDWR) for fluoride are submitted to the U.S. Environmental Protection Agency (EPA) in response to the March 29, 2010, request for public comments (Federal Register 2010). These comments are not to be considered a comprehensive review 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.

1. Current drinking water standards for fluoride

The maximum contaminant level goal (MCLG) is defined as 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 2006a). The enforceable level, the maximum contaminant level (MCL), is the "highest level of a contaminant that is allowed in drinking water" and is based on the MCLG (EPA 2006a). For fluoride, the MCLG and MCL are both set at 4 mg/L (EPA 2006a; Federal Register 2010). In March 2006, the National Research Council concluded that the present value of the MCLG (4 mg/L) is not protective of human health (NRC 2006a); based on the NRC's finding, the enforceable MCL must also be considered not protective.

By the usual philosophy of human health risk assessment, and in keeping with EPA's own definition of the MCLG, EPA should identify a level of fluoride in drinking water "at which no known or anticipated adverse effect on the health" of any person in the population is expected to occur, and which allows "an adequate margin of safety" to account for extremely sensitive or susceptible individuals or extremely high intake of drinking water. Therefore, it is surprising that EPA states that "the Agency does not believe a revision to the NPDWR for fluoride is appropriate at this time" (Federal Register 2010) due to various evaluations and assessments now in progress. EPA should have instituted interim values for the MCLG and MCL in 2006, and certainly by now, rather than leaving the NPDWR at a value that the NRC has found to be unsafe for human health. For example, lowering the MCLG and MCL by a factor of 10 from a value known to be not protective would at least provide a somewhat lower risk to human health while a more complete risk assessment is carried out.

EPA considers fluoride to be "unique" because of its presumed beneficial effects at "low" exposure levels and because it is "voluntarily added to some drinking water systems as a public health measure for reducing the incidence of cavities among the treated population" (Federal Register 2010). Note that "some drinking water systems" includes water supplies for more than 184 million people, or more than 60% of the U.S. population (CDC 2009). EPA should consider that situation as extra incentive to be absolutely certain that its MCLG and MCL for fluoride are "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 2006a). EPA should note 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), and EPA should be aware that its reference to a "treated population" acknowledges this use of drinking water systems to deliver a drug to entire populations. In this context, EPA should remember that many people consume more fluoride from tap water than from either non-prescription (toothpaste) or prescription (tablets or lozenges) fluoride sources, 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.

EPA should also note that its pesticide tolerances for sulfuryl fluoride (SO_2F_2), with respect to fluoride anion, are based on the MCL for fluoride in drinking water, specifically, on a reference dose (RfD) of 8 mg/day, which assumes a consumption of 2 L/day of water containing fluoride at the MCL of 4 mg/L (Federal Register 2005; EPA 2006b). This situation should also provide additional incentive for EPA to be certain that its MCLG and MCL for fluoride are adequately protective. If the drinking water standards are not protective (NRC 2006a), then it follows that the pesticide tolerances for sulfuryl fluoride are also not protective.

2. Exposure to fluoride

Fluoride exposures come from a variety of sources, including drinking water, toothpaste and other dental products, some soils and plants, occupational exposures, pesticides, pharmaceuticals, and industrial air pollution. The National Research Council's 2006 report on Fluoride in Drinking Water includes an extensive survey and summary of fluoride exposures in the U.S. from all sources (NRC 2006a).

For most of the U.S. population, the single largest source of fluoride exposure is municipal tap water, including tap water used directly, beverages and foods prepared with municipal tap water either at home or in restaurants, and commercial beverages and processed foods prepared with municipal tap water (NRC 2006a). For a water fluoride level of 1 mg/L (1 ppm), estimated average exposures to fluoride from all sources range from about 0.03 mg/kg/day (mg of fluoride per kg of body weight per day) for adults and nursing infants to 0.09 mg/kg/day for non-nursing infants (especially infants fed formula prepared with fluoridated tap water). Note that these are estimated *average* exposures. For individuals with high tap water consumption (discussed by NRC 2006a), total fluoride exposures can exceed 0.1 mg/kg/day for some adults and may reach 0.2 mg/kg/day for some infants. EPA itself has calculated "aggregate" exposures to fluoride (exposures from all sources) ranging from 0.043 mg/kg/day for adults to 0.209 mg/kg/day for infants less than 1 year old (Federal Register 2005).

Infants have a very high fluid intake per unit body weight, such that infants whose formula is prepared with fluoridated tap water can receive very high fluoride exposures. EPA (2004a) reports that the mean consumption of community (tap) water by all infants less than 6 months old is 50 mL/kg/day (mL of water per kg body weight per day), with a 90th percentile of 146 mL/kg/day. These water intakes would provide fluoride intakes of 0.035-0.06 mg/kg/day and 0.10-0.18 mg/kg/day for mean and 90th percentile persons, respectively, based on fluoride concentrations of 0.7-1.2 mg/L in drinking water. If only "consumers" are included (i.e., babies not consuming any tap water are excluded), the mean water intake is 95 mL/kg/day, and the 90th

percentile is 184 mL/kg/day; these water intakes would provide fluoride intakes of 0.067-0.11 mg/kg/day and 0.13-0.22 mL/kg/day, respectively. Erdal and Buchanan (2005) estimated total fluoride intakes of infants to be 0.11 ("central tendency") and 0.20 ("reasonable maximum exposure") mg/kg/day in fluoridated areas and 0.08 and 0.11 mg/kg/day, respectively, in nonfluoridated areas. In one of the few studies to evaluate actual individual intakes of fluoride from all sources, Warren et al. (2009) report individual fluoride intakes (from all sources) in excess of 0.2 mg/kg/day for some infants.

Sohn et al. (2009) used survey data from the National Health and Nutrition Survey (NHANES III) and default assumptions about fluoride concentrations in various foods and beverages to estimate fluoride ingestion by U.S. children aged 1-10 years. The estimated mean fluoride intakes were 0.045, 0.045, and 0.037 mg/kg/day for children ages 1-2, 3-5, and 6-10, respectively, living in areas with fluoridated water (1 mg/L fluoride). The estimated 90th percentiles for the same age groups were 0.090, 0.091, and 0.071 mg/kg/day. Note that these estimates are expected to be low, since they do not include water used in reconstitution (e.g., of juices) or cooking, or fluoride intake from solid food or toothpaste. For example, toothpaste could provide an additional average contribution of 0.02-0.04 mg/kg/day to the fluoride intake of young children; Sohn et al. 2009). Importantly, estimated mean fluoride intakes are lowest for children with high milk consumption (0.027, 0.024, and 0.019 mg/kg/day for the 3 age groups; milk has a very low fluoride content) and highest for children with high water consumption (0.066, 0.063, and 0.050 mg/kg/day). For children of all ages, estimated mean fluoride intakes are higher for African-Americans (0.050 mg/kg/day) than for whites (0.039 mg/kg/day), and higher for children of low socioeconomic status (low SES; 0.045 mg/kg/day) than for high SES (0.036 mg/kg/day). The likely explanation given for these findings is the lower milk consumption and higher water consumption among African-American or low-SES children than among white or high-SES children (Sohn et al. 2009). The authors conclude that in a given fluoridated area, some children "may be ingesting significantly more fluoride than others" (Sohn et al. 2009). Estimates of the higher levels of intake (e.g., 90th percentile) by race/ethnicity or SES were not provided.

In addition to infants and small children, the NRC (2006a) identified several sizeable subgroups of the U.S. population that also require special consideration due to above-average fluoride exposures. For example, athletes, outdoor workers, and military personnel—people with high activity levels—may consume 50-70 mL/kg/day (NRC 2006a). For fluoridated water (0.7-1.2 mg/L), this corresponds to a fluoride intake of 0.035-0.06 mg/kg/day (at 50 mL/kg/day) up to 0.049-0.084 mg/kg/day (at 70 mL/kg/day), just from water, without considering other sources of fluoride intake (NRC 2006a). Individuals of any age with diabetes insipidus may have water consumption as high as 150 mL/kg/day; this would provide a fluoride intake of 0.11-0.18 mg/kg/day just from drinking water (NRC 2006a).

As a point of comparison, EPA currently has a reference dose (RfD) for fluoride of 0.06 mg/kg/day (EPA 1989), based on preventing "objectionable" dental fluorosis in children. As described above and elsewhere (e.g., NRC 2006a), many infants and small children (among others) currently have fluoride intakes much greater than 0.06 mg/kg/day, indicating that current drinking water standards are not protective. At a water fluoride concentration equal to the MCLG and MCL, 4 mg/L, the *average* fluoride intake from all sources exceeds 0.06 mg/kg/day for all age groups, by as much as a factor of 4 for bottle-fed infants (NRC 2006a). Even at a

water fluoride concentration of 1 mg/L, the *average* intake by infants and children (the group susceptible to development of dental fluorosis) equals or exceeds 0.06 mg/kg/day (NRC 2006a); the only exception is nursing infants, whose water consumption is typically very low. Thus EPA's current drinking water standards (the MCLG and MCL) are not even consistent with EPA's own RfD for fluoride; they do not ensure that members of the vulnerable population will not have intakes above the RfD.

It is especially important to know that EPA's current MCLG and MCL for fluoride of 4 mg/L have been interpreted within the EPA to mean that water consumption of 2 L/day at the MCL (8 mg/day total from water alone, without consideration of other fluoride sources) is acceptable for all ages (Federal Register 2005; EPA 2006b), including infants. For example, for a 7-kg infant, EPA has interpreted the MCL to mean that an intake of 8 mg/day, or 1.1 mg/kg/day, is safe and acceptable. This intake is nearly 20 times EPA's stated RfD for fluoride. If MCLs are to be interpreted in this fashion, then EPA should go to great lengths to be certain that its standards will in fact protect the health of all individuals, especially infants on formula prepared with tap water and individuals of any age with high water consumption.

3. Basis for a new MCLG for fluoride

Once again, the maximum contaminant level goal (MCLG) is defined as 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 2006a). EPA must consider both the well-known and better studied adverse health effects of fluoride and the "anticipated" adverse health effects of fluoride, for which the data base may not be as complete as desired. This approach would be in keeping with the “precautionary principle”—in other words, "in the face of uncertain evidence it is important to act in a manner that protects public health" (Tickner and Coffin 2006). This approach would also help shift the emphasis in research to obtaining better information about the health effects of fluoride, as opposed to an attitude of inconclusive studies being equated to evidence of no effect (e.g., Cheng et al. 2007). If anything, EPA should require very high quality studies in support of any statement that a particular adverse health effect from fluoride exposure does not occur.

A few comments are in order regarding the interpretation of the available fluoride studies. 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 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 to fluoride than are most animal species that have been studied.

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, average intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006a). Sections 3.1-3.8 summarize briefly some (not all) of the adverse health effects, known and anticipated, that should be considered by EPA in its reevaluation of the drinking water standards for fluoride. Most of these effects have been reviewed in detail by the NRC (2006a), although the NRC did not specifically evaluate health risks over the whole range of fluoride intakes, and it did not attempt to identify a "safe" level of fluoride exposure from which to establish a new MCLG. Section 3.9 describes several of the high-risk population groups with respect to effects of fluoride exposure.

3.1. Dental fluorosis

Dental fluorosis (enamel fluorosis) is defined as mottling, staining, or pitting of the tooth surfaces due to disruption of the enamel maturation process; it ranges from very mild to moderate and severe and is associated with fluoride exposures during infancy and early childhood (NRC 2006a). The National Research Council considers severe dental fluorosis to be an adverse health effect and reports the general consensus in the literature that both severe and moderate dental fluorosis should be prevented (NRC 2006a). Health Canada (2009) considers moderate dental fluorosis to be an adverse effect. At the very least, the occurrence of dental fluorosis indicates overexposure to fluoride during infancy and early childhood, or an increased susceptibility to effects of fluoride, or both.

The American Dental Association has 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). This is an admission that dental fluorosis is undesirable, and that fluoridated tap water is not "safe" for all individuals. A study by the University of Iowa (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).

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. However, the failure to look for adverse health effects does not demonstrate the absence of adverse health effects.

The Iowa study has found that the ranges of daily fluoride 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 to 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. Warren et al. (2009) have reported no association between fluoride intake and caries status in this cohort (see Section 4 of these comments). 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 a 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, see also Section 4 of these comments), 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. CDC (2005) reports that for fluoridated and nonfluoridated populations combined, 23% of persons ages 6-39 have dental fluorosis, including 2.45% with moderate/severe fluorosis. Blacks are affected more commonly than whites (32.88% vs. 19.88%; CDC 2005).

3.2. Skeletal fluorosis

Skeletal fluorosis refers to bone and joint effects ranging from increased bone density (stage I) to chronic joint pain, arthritic symptoms, calcification of ligaments, and osteosclerosis of cancellous bones (stage II) to excessive calcification in joints, ligaments, and vertebral bodies, muscle wasting, and neurologic deficits due to spinal-cord compression (stage III, "crippling" skeletal fluorosis; NRC 2006a). EPA's current MCLG and MCL for fluoride is intended to protect against "crippling" skeletal fluorosis (Federal Register 2010). The National Research Council indicated that the current MCLG is not protective of human health, and a lower value should be set to provide protection against stage II skeletal fluorosis, not just stage III (NRC 2006a).

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 2006a). Bone fluoride concentrations, radiologic changes, and symptoms are not clearly correlated (Franke et al. 1975), and most U.S. studies do not categorize cases by stage. Recent case reports include fluorosis attributed to excessive ingestion of tea or toothpaste (Whyte et al. 2005; Hallanger Johnson et al. 2007; Kurland et al. 2007). 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.

3.3. Increased risk of bone fractures

The National Research Council indicated that the current MCLG is not protective of human health, and a lower value should be set to provide protection against increased risk of bone fracture (NRC 2006a). Specifically, the NRC (2006a) 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) 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).

The Agency for Toxic Substances and Disease Registry 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 2006a) indicate that the ATSDR's MRL is also not protective enough. 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) 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.

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). 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.

3.4. Carcinogenicity

The EPA 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). 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 2006a). 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 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.

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." 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).

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. Fluoride may exert a promotional effect, in addition to or instead of an initiation effect (NRC 2006a), in which case exposure during the "lag time" may be (or may continue to be) important, but this too could be obscured by looking only at a cumulative measure of fluoride exposure.

In a letter, not a research article, Douglass and Joshipura (2006) warn against putting too much stock in the results reported by Bassin et al. (2006), indicating that their own findings do not support Bassin's results. It should be noted that Douglass approved Bassin's dissertation (Bassin 2001), on which her paper was based, and both Douglass and Joshipura were coauthors on an earlier paper by Bassin et al. (2004) describing the exposure analysis used in the study. The dissertation (Bassin 2001) and peer-reviewed paper (Bassin et al. 2006) contain essentially the same results. Douglass and Joshipura mention an analysis of the fluoride content of bone specimens from the osteosarcoma patients and a lack of association between bone fluoride concentration and excess risk of osteosarcoma; however, fluoride concentration in bones of diagnosed patients constitutes a measure of cumulative fluoride exposure to the time of diagnosis

or treatment, and would not necessarily be expected to be correlated with the risk of osteosarcoma.

The results promised by Douglass and Joshipura (2006) constitute the Harvard study referred to by both the NRC (2006a) and EPA (Federal Register 2010). After more than four years, these results still have not been published, have not been peer-reviewed, and are not available for scientific examination or discussion. EPA should not continue to wait for a study that might never be published.

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 EPA in its evaluation of drinking water standards for fluoride.

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.

3.5. 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 the other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006a); 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 2006a). Thus, 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 2006a) and thus are also at risk for genotoxic effects.

3.6. Endocrine effects

The NRC (2006a) 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 2006a) Of particular concern is an inverse correlation between subclinical maternal 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). Steingraber (2007) has described the decrease in age at puberty of U.S.

girls and the associated increased risk of breast cancer. Calcium deficiency induced or exacerbated by fluoride exposure may contribute to other health effects (NRC 2006a).

3.7. 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 2006a; Coplan et al. 2007). Approximately 90% of people on fluoridated water are on systems using silicofluorides (NRC 2006a). 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), has not been adequately studied (NRC 2006a). 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) also increases the leaching of lead from plumbing fixtures into drinking water (Maas et al. 2005; 2007). A recent Congressional investigation has discussed the failure of the Centers for Disease Control and Prevention (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).

Although EPA has done some studies of the water chemistry (reviewed by NRC 2006a; Coplan et al. 2007), EPA has not examined the biological effects of silicofluorides. Very little toxicological research has been done specifically with silicofluorides. EPA should be certain that its drinking water standards for fluoride are protective of effects due to silicofluorides, interactions of fluoridating agents with disinfection agents, and any possible contribution to increased lead exposure, uptake, or retention. 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 2006a).

3.8. 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.

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 2006a). 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 2006a). 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).

3.9. High-risk population groups

A number of population subgroups have been identified as being at higher risk than usual for health effects from fluoride, due to higher exposure to fluoride, reduced excretion (higher retention) of fluoride, or increased susceptibility to biological effects from fluoride (NRC 2006a). For example, the elderly and people with reduced kidney function could have reduced excretion and consequent higher retention and accumulation of fluoride (NRC 2006a). Revised drinking water standards should be protective for all of these at-risk persons.

People with high water consumption for any of a variety of reasons will have high fluoride intakes if their water is fluoridated (see Section 2 above). These groups include people with high activity levels or working outdoors in hot climates, as well as people with medical conditions such as diabetes insipidus or inadequately controlled diabetes mellitus. Persons may also have high fluoride intakes from nonwater sources (e.g., toothpaste ingestion, tea consumption, occupational exposure). Pesticide tolerances based on the current MCL for fluoride (see Sections 1 and 2 above) could also result in high fluoride exposures.

Of special concern are infants and young children who are fed formula prepared with fluoridated water. Because of their very high fluid intake with respect to body weight, the very young are extremely likely to have high fluoride intakes. Breast feeding is not practical or even possible for some families (e.g., adoptive families, many working mothers). Ready-to-feed formula is generally lower in fluoride than formula made with fluoridated water, but may be unaffordable by many families. In addition, many, if not most, parents of infants and young children are probably not aware that fluoridated tap water is not recommended for use in preparation of infant formula (ADA 2006), or they may be unable to afford bottled water for that purpose.

Also of special concern should be institutionalized persons, persons with minority or low socioeconomic status, and persons with dietary inadequacies, especially calcium or iodine deficiencies. Iodine deficiency appears to make people more susceptible to thyroid effects from fluoride (NRC 2006a). As estimated by Sohn et al. (2009) for children, low intake of dairy products often coincides with higher fluoride intake (due to higher water intake); in addition, fluoride exposure may increase the calcium requirement, thus exacerbating a calcium deficiency

(NRC 2006a). Calcium deficiency may contribute to retention of heavy metals such as lead and to consequent toxicity (Goyer 1995) or to other effects such as nutritional rickets (NRC 2006a).

As described elsewhere (e.g., Sohn et al. 2009; NRC 2006a), minority status and low socioeconomic status are often associated with lower milk consumption, higher water consumption, and consequent higher likelihood of both calcium deficiency and high fluoride intake. Low income families and institutionalized individuals have far fewer options available to them, in terms of water sources or food sources. These people may have higher than average fluoride intakes, and due to nutritional inadequacies, they may also be at higher risk of effects from fluoride exposure.

4. Is water fluoridation beneficial?

Given that close to two-thirds of the U.S. population is served with fluoridated tap water, that fluoridated tap water is the primary source of fluoride intake for most individuals, and that fluoride intake for many persons exceeds levels associated with adverse health effects, it is essential that the practice of water fluoridation be examined in any serious discussion of drinking water standards for fluoride. The goal of community water fluoridation, i.e., "voluntary" addition of fluoride to drinking water, is to provide a dental health benefit to individuals and to the population generally, as EPA notes (Federal Register 2010). (Remember that "voluntary" refers to the action of the water authority, local government, or other decision-making entity, not to individual consumers or residents.) 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). Apart from the obvious ethical issues involved in this approach, the question of whether water fluoridation actually produces a benefit requires attention.

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 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 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 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.

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; other types of caries were not addressed in the paper). A number of sources (reviewed by NRC 2006a), including the CDC (2001), 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."

Two recent papers, whose authors include leading U.S. dental health experts, 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).

Thus, the best recent data available indicate little or no beneficial effect of water fluoridation on oral health. The EPA should not assume or suppose beneficial effects of community water

fluoridation in its assessment of fluoride exposure and toxicity or of what constitutes a safe level of fluoride or silicofluorides in drinking water.

5. Summary

As described above, EPA's current drinking water standards for fluoride are not protective of human health and are not consistent with its own (not fully protective) reference dose for fluoride. Current fluoride exposures exceed EPA's reference dose and the ATSDR's analogous minimal risk level, especially for infants, young children, and people of any age with high water consumption. For noncancer effects, a new reference dose should be established that accounts for the known and anticipated adverse health effects of fluoride. New drinking water standards should be derived that are protective for both sensitive and severe effects and that allow an adequate margin of safety. The carcinogenicity and genotoxicity of fluoride should also be accounted for in setting adequately protective standards. Current data do not support a beneficial effect of ingested fluoride on the oral health of the population, and EPA should not let assumptions about beneficial effects of fluoride distract from its responsibility to protect the health of all members of the U.S. population.

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."

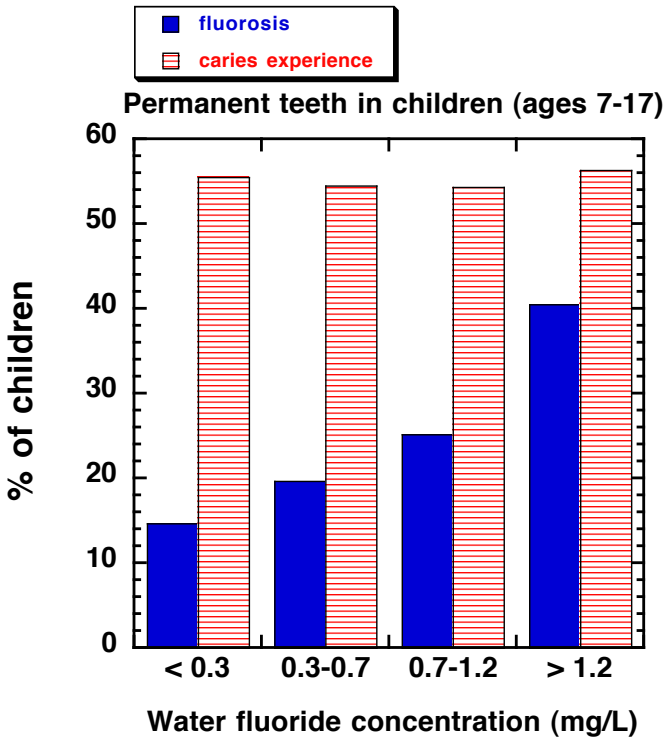

Fig. 1. Fluorosis prevalence and caries prevalence with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or caries experience. Numerical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

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