**Comments on**
**the Benefits and Safety of Water Fluoridation**

Prepared for the
Austin City Council

May 14, 2010

Kathleen M. Thiessen, Ph.D.
SENES Oak Ridge, Inc.,
Center for Risk Analysis
102 Donner Drive,
Oak Ridge, TN 37830
(865) 483-6111
kmt@senes.com

These comments on the benefits and safety of water fluoridation are submitted to members of the Austin (Texas) City Council in response to a request from Neil Carman, Ph.D. These comments are not to be considered a comprehensive review of water fluoridation issues.

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 was also the author of an Environmental Protection Agency report on fluoride toxicity in the 1980s.

## 1. Major issues

There are two major issues with respect to water fluoridation: (1) Is it beneficial? and (2) Is it safe? If it is not beneficial to individuals and the population, there is obviously no justification whatsoever for the practice. If the practice is not safe, for all members of the population (including infants, children, the elderly, the ill, sensitive or susceptible individuals) over the entire range of exposures, then, again, the practice is not justified.

## 2. Is water fluoridation beneficial?

The goal of community water fluoridation is to provide a dental health benefit to individuals and to the population generally. 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).

**3. Is water fluoridation safe?**

To call water fluoridation "safe" would require demonstration from very high quality studies that fluoride in drinking water at the proposed concentration (or range of concentrations) will not harm any member of the affected populations. This requires consideration of both the wide range of fluoride exposures (intakes) expected in the population and the level of exposure at which adverse health effects have been observed or can be expected to occur.

In general, guidelines such as the Environmental Protection Agency's drinking water standards (USEPA 2006) are intended to protect all persons, including members of susceptible population subgroups, from contaminant exposures that could cause them harm, with an adequate margin of safety. A risk assessment for a chemical contaminant such as fluoride, therefore, should evaluate the contaminant intakes (mg/kg/day, i.e., mg of fluoride per kg body weight per day) associated with various adverse health effects and, if possible, identify an intake at or below which no one will experience any adverse health effect. When studies are less than ideal, it is necessary, in the interest of protecting health, to acknowledge the uncertainties and apply appropriate safety factors to ensure an adequate margin of safety. Some studies, for example, use sample sizes that are too small to be able to show a moderate effect; it is incorrect to assume that therefore there is no effect. Study populations are often grouped by community, water source, or fluoride concentration in the water, rather than by individual intake. This results in study groups with overlapping intakes and makes it difficult to detect dose response relationships that do in fact exist.

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

Typical assessments of fluoride intakes do not adequately account for the range of tap water consumption, which varies over at least an order of magnitude for U.S. residents, for a given age group (NRC 2006a). At Austin's average concentration of fluoride in drinking water (0.75 mg/L), some bottle-fed infants will have fluoride intakes in excess of 0.17 mg/kg/day; some adults in the general population will have fluoride intakes in excess of 0.04 mg/kg/day, while individuals of any age with diabetes insipidus (DI) will easily have fluoride intakes of 0.11 mg/kg/day. These estimated intakes are for fluoride from tap water only, without contributions from other sources (NRC 2006a).

A number of adverse health effects can be expected to occur in at least some individuals when estimated average intakes of fluoride are around 0.05 mg/kg/day or higher (NRC 2006a; 2009). For persons with iodine deficiency, intakes as low as 0.01-0.03 mg/kg/day could produce effects

(NRC 2006a). The NRC (2006a) did not specifically evaluate health risks over the whole range of fluoride intakes, but in several cases, the available information included exposures to fluoridated drinking water in the U.S. (0.7-1.2 mg/L).

The U.S. National Research Council (NRC 2006a) concluded that EPA's current drinking water standard (4 mg/L) is an unsafe concentration of fluoride in drinking water and is not protective of human health. The NRC did not attempt to identify a "safe" concentration, which obviously would be somewhere below 4 mg/L, if one exists. Common risk assessment practice would require identifying a "safe" level of fluoride intake (to protect all members of the population) and setting a corresponding maximum acceptable concentration in drinking water "at level at which no known or anticipated adverse effect on the health of persons occurs and which allows an adequate margin of safety" (USEPA 2006). This would be at least a factor of 10 below the "unsafe" concentration of 4 mg/L (NRC 2006a) and could be lower, or even 0 (Carton 2006).

At the very least, there is more than sufficient evidence to support a precautionary approach of limiting fluoride exposure (Tickner and Coffin 2006). To wait until there is absolute proof of adverse health effects due to fluoride exposure is to continue to provide an incentive not to do good studies. The Austin City Council should take the responsible approach, which is to require a high level of evidence that there are no adverse health effects before permitting, let alone encouraging, widespread and unmonitored exposure of the entire population, including many individuals belonging to high-risk subgroups.

## 4. Some health risks associated with fluoride exposures

### *4.1. 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 (NRC 2006a). 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). At the very least, this is an admission that dental fluorosis is undesirable, and that fluoridated tap water is not "safe" for all individuals. 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.

In the Iowa study, the ranges of daily intake for children with and without fluorosis overlap considerably (Warren et al. 2009). For children in this cohort with intakes below 0.04 mg/kg/day

for their first 3 years of life, fluorosis rates for both maxillary central incisors ranged from 12 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. This is the same cohort for which Warren et al. (2009) reported no association between fluoride intake and caries status (discussed earlier). Levy et al. (2009) have reported weak relationships in this same cohort between fluoride intake during childhood and bone mineral concentration and bone mineral density as measured by dual-energy x-ray absorptiometry (DXA) at age 11, but so far they have not reported the dental fluorosis status in children with or without bone effects related to fluoride intake.

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

### *4.2 Carcinogenicity*

The Austin City Council 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 (2006a) committee unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed." Referring to the animal studies, the committee also said that "the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans." The committee also discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007).

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

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). The contradictory results promised by Douglass and Joshipura (2006) have not been published to date, have not been peer-reviewed, and are not available for scientific examination or discussion. It is also important to note that the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans as reported by Bassin et al. (2006), and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas.

*4.3. Genotoxicity*

A genotoxic chemical is one that can damage the genetic material (genes and chromosomes) of cells, which 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). 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; 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. Human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

*4.4. Skeletal fluorosis*

Skeletal fluorosis refers to bone and joint effects ranging from increased bone density (stage 1) 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 2006). Bone fluoride concentrations in the ranges reported for stage II and III 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.

*4.5. Increased risk of bone fractures*

An increased risk of bone fractures is associated with estimated average daily intakes of 0.05-0.08 mg/kg/day (NRC 2006a). 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). Animal studies have shown increased brittleness of bones with increased fluoride exposure (Clark and Mann 1938; Turner et al. 1997; 2001). Most studies have not addressed age-specific exposure. 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. are increasing (Khosla et al. 2003), but fluoride exposure has not been examined as a possible cause.

*4.6. Male reproductive effects*

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

*4.7. 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). Thyroid dysfunction and Type II diabetes presently pose substantial health concerns in the U.S. 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).

*4.8. 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 (Coplan et al. 2007).

**5. Additional comments**

*5.1. Comparison of fluoride exposures in animal and human studies*

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 than most animal species that have been studied.

*5.2. Early fluoride studies in Texas*

The Austin City Council may be interested in some early studies of fluoride exposures carried out in the towns of Bartlett and Cameron, Texas, to demonstrate the safety of fluoride exposures. These studies ostensibly compared towns with natural fluoride concentrations of 8 and 0.4 mg/L (Leone et al. 1954a,b; 1955a,b), although in fact the high-fluoride town (Bartlett) was partially defluoridated (to about 1.2 mg/L) approximately 18 months before the major comparison of

health endpoints was made (Maier 1953). This fact is omitted in the radiographic study (Leone et al. 1955a) and dismissed as irrelevant in the other reports. However, urine fluoride concentrations measured in the high-fluoride town decreased considerably during the time following defluoridation (Likins et al. 1956), indicating significant mobilization of fluoride from the bones. By the time the 1953 examinations were conducted, the differences between the two groups of participants would have been substantially smaller, especially for any endpoints that depend on current fluoride balance. In addition, some long-term effects of fluoride (e.g., bone changes) are also reversible to some extent in that length of time (Roholm 1939).

Thus comparisons were not made between people consuming 0.4 and 8 mg/L fluoride, but between people consuming 0.4 and approximately 1.2 mg/L fluoride, after enough time had elapsed for the group formerly exposed at 8 mg/L to experience considerable mobilization of fluoride and consequent decrease in physiological fluoride concentrations. People who had moved from the towns were also examined, and included in some of the tabulations of results, but no information on their recent fluoride exposures was reported. Most people who moved away from Bartlett would have moved to areas with substantially lower fluoride exposures. Also, no information was given about whether people drank tap water or bottled water (NRC 1977).

Given these conditions, it is not surprising that little or no difference in most health endpoints was found between Bartlett and Cameron. However, notable differences were found in irreversible endpoints: a higher rate of dental fluorosis in participants who had lived in Bartlett during childhood (Leone et al. 1954b), a higher rate of edentulousness (complete tooth loss) in Bartlett residents (31 of 76 in Bartlett vs. 16 of 80 in Cameron; Zimmermann et al. 1955; Russell 1957), and a higher death rate among study participants during the 10-year period (14 of the original 116 participants in Bartlett vs. 4 of the original 121 participants in Cameron; Leone et al. 1954a,b). The study's authors judged the difference in the age-corrected death rates in the two towns to be not statistically significant (Leone et al. 1954a,b). A reanalysis by the American Medical Association indicated a statistically significant difference in mortality, but dismissed the importance of the finding (AMA 1957; NRC 1977). The NRC (1977) discussed the uncertainty in the findings of this and other fluoridation studies and included further study of mortality ratios evaluated by cause of death among their recommendations, something that has not been pursued.

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."

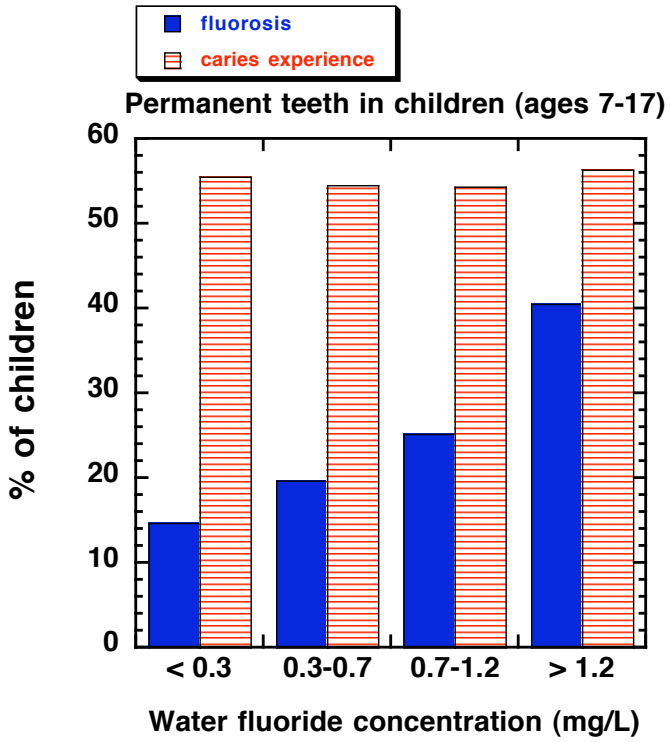


Fig. 1. Fluorosis prevalence and caries prevalence with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or caries experience. Numerical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

**References**

ADA (American Dental Association). 2005. Fluoridation facts. Chicago, IL: American Dental Association. [Available: http://www.ada.org/public/topics/fluoride/facts/index.asp]

ADA (American Dental Association). 2006. ADA Positions & Statements: Interim Guidance on Fluoride Intake for Infants and Young Children. November 8, 2006. [Available: http://www.ada.org/prof/resources/positions/statements/fluoride_infants.asp]

Alarcón-Herrera, M.T., Martín-Domínguez, I.R., Trejo-Vázquez, R., and Rodriguez-Dozal, S. 2001. Well water fluoride, dental fluorosis, and bone fractures in the Guadiana Valley of Mexico. Fluoride 34:139-149.

Alvarez, J.O. 1995. Nutrition, tooth development, and dental caries. Am J Clin Nutr 61S:410S-416S.

Alvarez, J.O., and Navia, J.M. 1989. Nutritional status, tooth eruption, and dental caries: a review. Am J Clin Nutr 49:417-426.

AMA (American Medical Association). 1957. Proceedings of the House of Delegates. Clinical Session, Philadelphia, PA, December 3-5, 1957.

Bassin, E.B., Wypij, D., Davis, R.B., and Mittleman, M.A. 2006. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control. 17(4):421-428.

Björnhagen, V., Höjer, J., Karlson-Stiber, C., Seldén, A.I., and Sundbom, M. 2003. Hydrofluoric acid-induced burns and life-threatening systemic poisoning: Favorable outcome after hemodialysis. Clinical Toxicology 41(6):855-860.

Carton, R.J. 2006. Review of the 2006 United States National Research Council Report: Fluoride in Drinking Water. Fluoride 39(3):163-172.

CDC (Centers for Disease Control and Prevention). 2001. Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. Morbidity and Mortality Weekly Report 50(RR-14). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

CDC (Centers for Disease Control and Prevention). 2005. Surveillance for Dental Caries, Dental Sealants, Tooth Retention, Edentulism, and Enamel Fluorosis—United States, 1988-1994 and 1999-2002. Morbidity and Mortality Weekly Report 54(SS3):1-43. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

CDC (Centers for Disease Control and Prevention). 2006. Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation--United States, 2003-2005. Morbidity and Mortality Weekly Report 55(40):1089-1092. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Cheng, K.K., Chalmers, I., and Sheldon, T.A. 2007. Adding fluoride to water supplies. BMJ 335:699-702.

Clark JD, Mann EH. 1938. A study of the occurrence of fluorine in the drinking water of New Mexico and the menace of fluorine to health. The University of New Mexico Bulletin, Chemistry Series 2(5):3-23.

Coplan MJ, Patch SC, Masters RD, Bachman MS. 2007. Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals. NeuroToxicology 28:1032-1042.

Cross, D.W., and R.J. Carton. 2003. Fluoridation: A violation of medical ethics and human rights. Int. J. Occup. Environ. Health 9(1):24-29.

Danielson, C., Lyon, J.L., Egger, M., and Goodenough, G.K. 1992. Hip fractures and fluoridation in Utah's elderly population. JAMA 268:746-748.

Desai, V.K., Solanki, D.M., and Bansal, R.K. 1993. Epidemiological study on goitre in endemic fluorosis district of Gujarat. Fluoride 26:187-190.

Douglass, C.W., and Joshipura, K. 2006. Caution needed in fluoride and osteosarcoma study. Cancer Causes Control 17:481-482 [letter].

Featherstone JDB. 2000. The science and practice of caries prevention. JADA 131:887-899.

Franke J, Rath F, Runge H, Fengler F, Auermann E, Lenart GL. 1975. Industrial fluorosis. Fluoride 8:61-85.

Graham, J.R., and Morin, P.J. 1999. Highlights in North American litigation during the twentieth century on artificial fluoridation of public water supplies. J. Land Use & Environmental Law 14(2):195-242.

Hallanger Johnson JE, Kearns AE, Doran PM, Khoo TK, Wermers RA. 2007. Fluoride-related bone disease associated with habitual tea consumption. Mayo Clin Proc 82:719-724.

Hong, L., Levy, S.M., Broffitt, B., Warren, J.J., Kanellis, M.J., Wefel, J.S., and Dawson, D.V. 2006a. Timing of fluoride intake in relation to development of fluorosis on maxillary central incisors. Community Dent Oral Epidemiol 34:299-209.

Hong, L., Levy, S.M., Warren, J.J., Broffitt, B., and Cavanaugh, J. 2006b. Fluoride intake levels in relation to fluorosis development in permanent maxillary central incisors and first molars. Caries Research 40:494-500.

Iida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.

Jooste, P.L., Weight, M.J., Kriek, J.A., and Louw, A.J. 1999. Endemic goitre in the absence of iodine deficiency in schoolchildren of the Northern Cape Province of South Africa. Eur J Clin Nutr 53:8-12.

Khosla S, Melton LJ III, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL. 2003. Incidence of childhood distal forearm fractures over 30 years. JAMA 290:1479-1485.

Kishi, K., and Ishida, T. 1993. Clastogenic activity of sodium fluoride in great ape cells. Mutation Research 301:183-188.

Komárek, A., Lesaffre, E., Härkänen, T., Declerck, D., and Virtanen, J.I. 2005. A Bayesian analysis of multivariate doubly-interval-censored dental data. Biostatistics 6(1):145-155.

Kurland ES, Schulman RC, Zerwekh JE, Reinus WR, Dempster DW, Whyte MP. 2007. Recovery from skeletal fluorosis (an enigmatic, American case). J Bone Mineral Res 22:163-170.

Leone NC, Shimkin MB, Arnold FA Jr, Stevenson CA, Zimmermann ER, Geiser PB, Lieberman JE. 1954a. Medical aspects of excessive fluoride in a water supply. A ten-year study. Pp. 110-130 in Fluoridation as a Public Health Measure, J.H. Shaw, ed. Washington, DC: American Association for the Advancement of Science.

Leone NC, Shimkin MB, Arnold FA Jr, Stevenson CA, Zimmermann ER, Geiser PB, and Lieberman JE. 1954b. Medical aspects of excessive fluoride in a water supply. Public Health Rep 69:925-936.

Leone NC, Stevenson CA, Hilbish TF, Sosman MC. 1955a. A roentgenologic study of a human population exposed to high fluoride domestic water: A 10 year study. Am J Roentgenol Radium Ther Nucl Med 74:874-875.

Leone NC, Arnold FA Jr, Zimmermann ER, Geiser PB, Lieberman JE. 1955b. Review of the Bartlett-Cameron survey: A ten year fluoride study. JADA 50:277-281.

Levy, S.M., Eichenberger-Gilmore, J., Warren, J.J., Letuchy, E., Broffitt, B., Marshall, T.A., Burns, T., Willing, M., Janz, K., and Torner, J.C. 2009. Associations of fluoride intake with children's bone measures at age 11. Community Dent Oral Epidemiol 37:416-426.

Li, X.S., Zhi, J.L., and Gao, R.O. 1995. Effect of fluoride exposure on intelligence in children. Fluoride 28:189-192.

Likins RC, McClure FJ, Steere AC. 1956. Urinary excretion of fluoride following defluoridation of a water supply. Public Health Rep 71:217-220.

Lin, F.F., Aihaiti, Zhao, H.X., Lin, J., Jiang, J.Y., Maimaiti, and Aiken. 1991. The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. IDD Newsletter 7:24-25.

Maier FJ. 1953. Defluoridation of municipal water supplies. J Am Water Works Assoc 45:879-888.

McDonagh, M., P. Whiting, M. Bradley, J. Cooper, A. Sutton, I. Chestnutt, K. Misso, P. Wilson, E. Treasure, and J. Kleijnen. 2000. A Systematic Review of Public Water Fluoridation. NHS Centre for Reviews and Dissemination, University of York, York, UK.

Neurath C. 2005. Tooth decay trends for 12 year olds in nonfluoridated and fluoridated countries. Fluoride 38:324-325.

NRC (National Research Council). 1977. Drinking Water and Health, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 2006a. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. [Available: http://www.nap.edu/catalog/11571.html]

NRC (National Research Council). 2006b. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2. [Available: http://www.nap.edu/catalog.php?record_id=11340]

NRC (National Research Council). 2009. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants: Volume 3. [Available: http://www.nap.edu/catalog.php?record_id=12741]

Penman, A.D., Brackin, B.T., and Embrey, R. 1997. Outbreak of acute fluoride poisoning caused by a fluoride overfeed, Mississippi, 1993. Public Health Reports 112:403-409.

Psoter, W.J., Reid, B.C., and Katz, R.V. 2005. Malnutrition and dental caries: A review of the literature. Caries Res 39:441-447.

Roholm K. 1937. Fluorine Intoxication: A Clinical-Hygienic Study, with a Review of the Literature and Some Experimental Investigations. London: H.K. Lewis & Co.

Román GC. 2007. Autism: Transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. J Neurological Sciences 262:15-26.

Russell AL. 1957. Fluoride domestic water and periodontal disease. Am J Public Health 47:688-694.

Shiboski CH, Gansky SA, Ramos-Gomez F, Ngo L, Isman R, Pollick HF. 2003. The association of early childhood caries and race/ethnicity among California preschool children. J Public Health Dentistry 63:38-46.

Short, E.M. 1944. Domestic water and dental caries: VI. The relation of fluoride domestic waters to permanent tooth eruption. J. Dent. Res. 23:247-255.

Steingraber, S. 2007. The Falling Age of Puberty in U.S. Girls: What We Know, What We Need to Know. San Francisco: The Breast Cancer Fund.

Sullivan K.M. 2009. Iodine deficiency as a cause of autism. J Neurological Sciences 276:202.

Susheela, A.K., Bhatnagar, M., Vig, K., and Mondal, N.K. 2005. Excess fluoride ingestion and thyroid hormone derangements in children living in Delhi, India. Fluoride 38:98-108.

Tickner, J., and Coffin, M. 2006. What does the precautionary principle mean for evidence-based dentistry? Journal of Evidence-Based Dental Practice 6(1):6-15.

Turner CH, Garetto LP, Dunipace AJ, Zhang W, Wilson ME, Grynpas MD, Chachra D, McClintock R, Peacock M, Stookey GK. 1997. Fluoride treatment increased serum IGF-1, bone turnover, and bone mass, but not bone strength, in rabbits. Calcif Tissue Int 61:77-83.

Turner CH, Hinckley WR, Wilson ME, Zhang W, Dunipace AJ. 2001. Combined effects of diets with reduced calcium and phosphate and increased fluoride intake on vertebral bone strength and histology in rats. Calcif Tissue Int 69:51-57.

USEPA (U.S. Environmental Protection Agency). 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Washington, DC: U.S. Environmental Protection Agency,

Office of Water, EPA 822-R-06-013. [Available: http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf]

Vohra, R., Velez, L.I., Rivera, W., Benitez, F.L., and Delaney, K.A. 2008. Recurrent life-threatening ventricular dysrhythmias associated with acute hydrofluoric acid ingestion: Observations in one case and implications for mechanism of toxicity. Clinical Toxicology 46:79-84.

Warren, J.J., Levy, S.M., Broffitt, B., Cavanaugh, J.E., Kanellis, M.J., and Weber-Gasparoni, K. 2009. Considerations on optimal fluoride intake using dental fluorosis and dental caries outcomes—A longitudinal study. J Public Health Dentistry 69:111-115.

Whyte MP, Essmyer K, Gannon FH, Reinus WR. 2005. Skeletal fluorosis and instant tea. Am J Med 118:78-82.

Wilson, P.M., and Sheldon, T.A. 2006. Muddy waters: evidence-based policy making, uncertainty and the "York review" on water fluoridation. Evidence & Policy 2(3):321-331.

Yang, Y., Wang, X., and Guo, X. 1994. Effects of high iodine and high fluorine on children's intelligence and the metabolism of iodine and fluorine [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi 15:296-298.

Zhang R, Niu Y, Du H, Cao X, Shi D, Hao Q, Zhou Y. 2009. A stable and sensitive testing system for potential carcinogens based on DNA damage-induced gene expression in human HepG2 cell. Toxicology in Vitro 23:158-165.

Zhao, L.B., Liang, G.H., Zhang, D.N., and Wu, X.R. 1996 . Effect of a high fluoride water supply on children's intelligence. Fluoride 29:190-192.

Zimmermann ER, Leone NC, Arnold FA Jr. 1955. Oral aspects of excessive fluorides in a water supply. JADA 50:272-277.