**Comments on**

**the U.S. EPA's Report**

**Fluoride: Dose-Response Analysis**

**for Non-Cancer Effects**

Prepared for the

U.S. Environmental Protection Agency

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## 1. Introduction

On 7 January 2011 the Environmental Protection Agency's (EPA) Office of Water (OW) released a new risk assessment for fluoride in drinking water. This was in response to recommendations set forth by a National Research Council (NRC) panel, as detailed in the 2006 report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*. Both the maximum contaminant level (MCL) and the maximum contaminant level goal (MCLG) for fluoride in drinking water are currently set at 4 mg/L, a level that the NRC panel determined is not protective of human health and "should be lowered" (NRC, 2006, p.10). The purpose of conducting a new risk assessment was to determine a more protective water standard and goal for fluoride in drinking water. In doing so, the NRC panel emphasized the need to consider susceptible subpopulations and characterize uncertainties and variability (NRC, 2006, p.10).

Another reason for OW to perform this risk assessment was that EPA's Office of Pesticide Programs (OPP) was under threat of lawsuit for basing its three health risk assessments for sulfuryl fluoride as a food fumigant solely on the safety of the fluoride MCLG of 4 ppm (EPA OPP, 2004, 2005, 2006). The NRC (2006) report stating that this MCLG was not protective of health thus undermined the basis of OPP's risk assessments. Objectors to EPA's approval of sulfuryl fluoride petitioned OPP for a Stay in June 2006 (Wallace, 2006). In 2010, Objectors were demanding a response to its Petition and Objections submitted in 2004 through 2006, and threatening legal action unless OPP responded to Objections and Stay (Wallace, Apr, Aug, Nov, 2010). Because OPP was unusually dependent on OW for performing the fluoride risk assessment, and because legal action was imminent, it was incumbent on OW to release its risk assessment at this time. Thus OW released this non-cancer risk assessment to also satisfy the needs of OPP.

While the MCL is a federally enforceable standard, the MCLG is "a health goal set at a concentration at which no adverse health effects are expected to occur" (NRC, 2006, p.1), and includes an adequate margin of safety to ensure that the entire population is protected from harmful effects. To establish an appropriate MCLG, current protocol is to first determine a safe reference dose (RfD), which is the amount of fluoride consumed per unit body weight per day (mg F/kg body weight/day) by the human population (including susceptible subpopulations) that is "likely to have no appreciable risk of deleterious health effects during a lifetime" (NRC, 2006, p.341). The current MCLG of 4 mg/L, established in 1986, was derived from a LOAEL of 20 mg F/day, as no RfD for fluoride was available at the time (NRC, 2006, p.345). However, this MCLG corresponds to an RfD of 0.114 mg F/kg/day (assuming a safety factor of 2.5 and an average adult body weight of 70 kg). This level was set to protect only against clinical stage III (crippling) skeletal fluorosis. The IRIS RfD, designed to protect against "objectionable" dental fluorosis, was set at 0.06 mg F/kg/day (EPA IRIS, 1989).

The new RfD offered by OW on 7 January 2011 is 0.08 mg/kg/day. Thus, while OW has ostensibly lowered the RfD for fluoride when compared with that associated with the current MCLG of 4 mg F/L (0.114 mg F/kg/day), OW has actually increased the RfD

over the previous IRIS RfD of 0.06 mg F/kg/day. OW claims that the proposed RfD of 0.08 mg F/kg/day will protect against severe dental fluorosis. In turn, OW claims, this RfD will also be "protective for the endpoints of severe fluorosis of primary teeth, stage II skeletal fluorosis and increased risk of bone fracture in adults" (EPA, 2010a, p. 107). Yet, despite the fact the scientific basis for this claim is riddled with uncertainties, OW has refused to incorporate an uncertainty factor in its calculations of the new RfD, meaning that no margin of safety has been allowed.

It was recommended by the NRC (2006) panel that "EPA should update the risk assessment for fluoride to include new data on health risks and better estimates of total exposure (relative source contribution) in individuals" (p. 352) in order to establish a new MCLG that would be protective of severe dental fluorosis, stage II skeletal fluorosis and bone fractures. However, NRC (2006) did not restrict OW from using other end points, and in the five years since this report was published, numerous scientific reports have added to the weight of evidence for additional health risks of concern (Appendix A), as discussed by the NRC panel. In particular, there have been at least 21 human studies, and at least 36 animal studies on the effects of fluoride on the brain and/or IQ. Of these, only one animal study found "no significant effect" (Whitford et al., 2009)[1]. While NRC (2006) reviewed only five studies investigating the relationship between lowered IQ and moderate-to-high exposure to fluoride, 24 such studies have now been conducted (See section 2.3 below), with 14 published since the NRC (2006) report (Appendix A). Thus, OW should have given serious consideration to additional end points for the purpose of determining an RfD and MCLG for fluoride.

In announcing this proposed RfD, EPA has made it clear that they have chosen a standard designed to protect the water fluoridation program. Fluoride is not an essential element, yet OW has nonetheless chosen to base the point of departure (POD) for estimation of a new RfD on the level of fluoride defined as "optimum" for caries prevention (0.05 mg/kg/day). OW has been so brazen as to not only eliminate any drinking water intakes less than this value as doses that may cause severe dental fluorosis (despite evidence to the contrary), but actually increased the POD by 0.02 mg/kg/day to "provide for a reasonable difference between it and the IOM (1997) intake" (EPA, 2010a, p. 101), and then added an additional 0.01 mg/kg/day to this value to account for fluoride intake from food. Interestingly, this is in contrast to IOM (1997), which stated that the AI is "for fluoride from all sources" (p. 302).

[1] A 2003 "abstract" of the Whitford et al. (2009) study was cited to counter the Mullenix et al. (1995) study in the ATSDR *Toxicological Profile for Fluoride, Hydrogen Fluoride and Fluorine* (2003). ATSDR wrote: "In a recent study only available as an abstract (Whitford et al., 2003), no significant alterations in performance on operant behavior tests were observed in female rats exposed to 2.9-11.5 mg F/kg/day in drinking water 7 months." (p. 111, online at http://www.atsdr.cdc.gov/ToxProfiles/tp11.pdf)

In a 7 January 2011 press release, Peter Silva, EPA Assistant Administrator for the OW, states that "EPA's new analysis will help us make sure that people benefit from tooth decay prevention while at the same time avoiding the unwanted health effects from too much fluoride" (HHS, 2011). This is in stark contrast to the NRC panel's statement that "EPA does not regulate or promote the addition of fluoride to drinking water" (NRC, 2006, p.53). It is also contrary to EPA's mandate to administer the national drinking water regulations, as its responsibility is to regulate contaminants only—i.e. "No national primary drinking water regulation may require the addition of any substance for preventative health care purposes unrelated to contamination of drinking water" (42 USC 300g-1(b)(11)).

## 2. Responses to EPA's Dose-Response Analysis

### *2.1. The methodology and rationale behind OW's proposed RfD are flawed.*

#### *2.1.1. Consideration of the adverse effects of fluoride should take precedence over any presumed benefits in OW's determination of an RfD and MCLG that are safe for the entire population.*

Determination of a safe RfD should be blind to benefits. These may play a part in moving from a scientifically determined MCLG to a federally enforceable MCL, which is frequently a compromise between the ideal (MCLG) and the practical (MCL), since the latter takes into account the costs of removal of natural pollutants such as arsenic. The MCLG for arsenic was set at zero by OW because it is a known human carcinogen, but its MCL was set at 0.01 ppm (10 ppb) as a compromise level because the costs of removal of naturally occurring arsenic down to zero would be prohibitive.

Fluoride is considered a contaminant by EPA, but OW has improperly offered it a protected status due to presumed benefits for oral health. OW states "it should be recognized that fluoride is a nutrient" (EPA, 2010b, p. 39). However, the misconception that fluoride is a nutrient that followed the publication of *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride* (IOM, 1997) was corrected in a 1999 joint letter from the Presidents of the National Academy of Sciences and the Institute of Medicine:

> "… First, let us reassure you with regard to one concern. Nowhere in the report is it stated that fluoride is an essential nutrient. If any speaker or panel member at the September 23rd [IOM] workshop referred to fluoride as such, they misspoke. As was stated in Recommended Dietary Allowances 10th Edition, which we published in 1989: "These contradictory results do not justify a classification of fluoride as an essential element, according to accepted standards. Nonetheless, because of its valuable effects on dental health, fluoride is a beneficial element for humans…" (Alberts and Shrine, 1999).

The Adequate Intake (AI) for fluoride was established by the IOM in 1997, prior to recognition that "the major anticaries benefit of fluoride is topical and not systemic" (NRC, 2006, p.16). This predominant mode of action is now also accepted by the Centers for Disease Control and Prevention (CDC, 2001), as well as numerous researchers (e.g. Zero et al., 1992; Rölla and Ekstrand, 1996; Featherstone, 1999; Limeback, 1999; Clarkson and McLoughlin, 2000; Warren and Levy, 2003; Fejerskov, 2004; Hellwig and Lennon, 2004; Pizzo et al., 2007; Cheng et al., 2007). Despite concerns raised by a Peer Reviewer (Den Besten, EPA, 2010c, pp. 16-17) that "The weight of evidence indicates that the primary mechanism by which fluoride protects against tooth decay is a topical effect" and that the "IOM's recommendation of an adequate intake value, at least relating to tooth decay, should be reassessed," OW has not corrected for these incongruities.

To demonstrate that a substance is an essential nutrient it is necessary to starve the animal of the substance in its diet and then show a disease accrues. This has not been done for fluoride. Not one single biochemical process in the animal body has been shown to need fluoride as a positive factor. To the contrary, many biochemical processes and mechanisms have been shown to be harmed by fluoride (Barbier et al., 2010).

Another indicator that fluoride is not a nutrient necessary for proper human development is the extremely low levels of fluoride that are found in human breast milk. For infants, nutritional status should be determined based on what is present, and at what levels, in breast milk. Breast milk averages only 0.007 mg F/L (NRC, 2006, p. 40). By labeling fluoride as a nutrient with AI requirements well above what is present in breast milk, OW is declaring that mother's milk is deficient as a complete nutritional source for infants.

The Institute of Medicine (IOM, 1997) states "Since the intake of fluoride by human milk-fed infants during this period of life (0-6 months) does not appear to significantly increase the risk of dental caries, fluoride from human milk is deemed adequate in early life (p. 302)." It is appreciated that IOM (1997) has been generous enough to deem human breast-milk "adequate" nutrition for infants, but it should be recognized by OW that the AI for fluoride (although no longer a reasonable concept due to the primarily topical nature of fluoride's action) established for infants 0-6 months is only 0.01 mg/day, based on the level of fluoride found in mother's milk (IOM, 1997, p. 302).

Human infants have evolved to be exposed to very little fluoride, as evidenced by the very low concentration of fluoride in breast milk. Despite maternal fluoride exposure, nursing children receive only 0.2% of the mother's fluoride intake (Şener et al, 2007). For example, mothers living in areas where the concentration of fluoride in water is naturally high (9 mg/L), and thus daily maternal intake of fluoride is also high (up to 37.2 mg/day), maintain breast milk with very low concentrations of fluoride (0.033 mg/L) (Opinya et al, 1991). Despite sharp increases of fluoride concentrations in blood plasma following a bolus ingestion of fluoride, the concentration of fluoride in breast milk remains relatively unchanged (Ekstrand et al, 1981, 1984). Thus there is likely an evolutionary mechanism that prevents infants from receiving high doses of fluoride from their mother's milk. The sensitive brains and bodies of breast-fed infants are therefore protected from the developmental effects of this toxin.

OW is viewed by scientists—both inside and outside of the Agency—as unwaveringly pro-fluoridation. It is unfortunate that OW contracted with Battelle (page ix) to perform the *Dose Response Analysis for Non-Cancer Effects*, as their history with the National Toxicology Program (NTP, 1990) in performing the rat studies for fluoride's carcinogenicity remains extremely controversial. OW has allowed the notion that fluoride is systemically beneficial to cloud its judgment on the safe limits of fluoride exposure for the American people, as it has applied absolutely no margin of safety in determining a new RfD for fluoride.

By choosing an uncertainty factor of 1 (i.e. no uncertainty) for fluoride, EPA's OW has sharply deviated from it practice for other substances. Contrast this with the uncertainty

factors of 30 and 100, used for the determination of the RfDs for the essential elements molybdenum and chromium III, respectively (EPA IRIS, 1993; 1998). Even though "a long-term study in a human population" was reviewed for molybdenum, EPA still used an uncertainty factor of 3 "for protection of sensitive populations," as well as a factor of 10 for the use of a LOAEL instead of a NOAEL. Despite the critical importance of zinc for the human body, the use of principal studies that were "well-conducted clinical studies with relevant biochemical parameters investigated in both males and females," and high confidence in the database—EPA still chose an uncertainty factor of 3 for zinc "to account for variability in susceptibility in human populations" (EPA IRIS, 2005). OW's refusal to include an uncertainty factor in the determination of an RfD for a non-essential element like fluoride, in order to protect an ill-conceived and presently invalid AI is neglectful and highly questionable.

The following quote makes it very clear that the EPA's determination of the RfD (and thence the MCLG) has been influenced by the need to protect the fluoridation program:

> The RfD is an estimate of the fluoride dose that will protect against severe dental fluorosis, clinical stage II skeletal fluorosis and skeletal fractures *while allowing for a fluoride exposure adequate to protect against tooth decay for children and adults.* (our emphasis) (EPA, 2010a, p. ii)

As a result of this pre-conceived agenda, the OW's determination of a *safe* RfD has not been an honest scientific exercise. Key assumptions were chosen, and data were selected or ignored (such as the voluminous evidence that fluoride damages the brain), in an effort to protect the fluoridation program rather than meeting the primary obligation of protecting the American people from harm.

OW appears to have accepted uncritically the highly exaggerated claims from fluoridation promoters, such as the CDC's Oral Health Division, that swallowing fluoride reduces tooth decay. OW needs to examine the science that supposedly supports such claims before bending normal procedures to protect this program.

For example, the press release issued jointly by the DHHS and EPA on Feb 7, 2011, states that the "The Centers for Disease Control and Prevention named the fluoridation of drinking water as one of the 10 great public health achievements of the 20$^{th}$ Century." It is embarrassing that the EPA is willing to go along with this propagandistic puff-piece from the CDC's Oral Health Division (whose primary purpose is to promote fluoridation) without examining the paper on which the statement was based (CDC, 1999b). The paper did not receive external peer review, and was already six years out of date on health studies when published. Figure 1 (CDC, 1999a) purportedly demonstrates that tooth decay was coming down amongst 12-year-olds in the U.S. because the percentage of Americans drinking fluoridated water had increased over the same period (1960s-1990s).

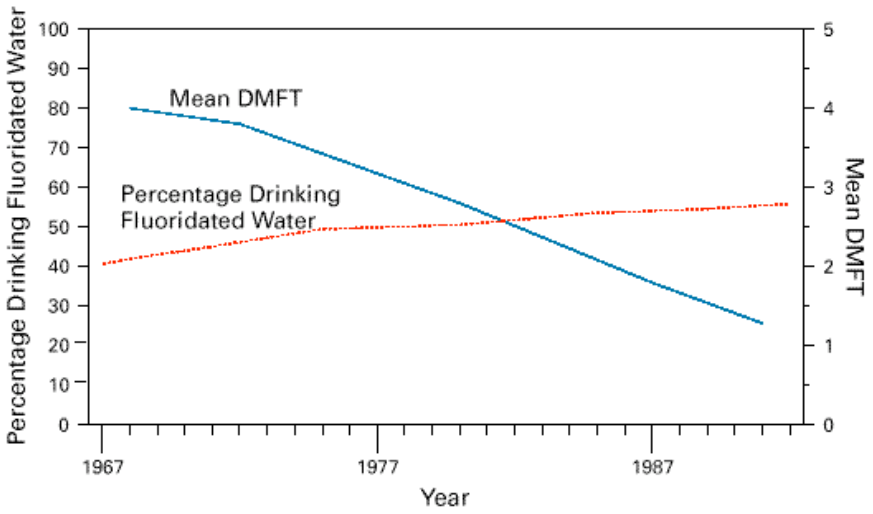


Figure 1. Percentage of population residing in areas with fluoridated community water systems and mean number of decayed, missing (because of caries), or filled permanent teeth (DMFT) among children aged 12 years—U.S., 1967-1992. Source: CDC, 1999.

This declaration was not only amateurish in the extreme, but is easily refuted by further examination of data from the World Health Organization (WHO). These data, when plotted graphically in the same manner as the CDC (1999a) plot, indicate that the same or greater declines in tooth decay in 12-year-olds has occurred in many non-fluoridated countries over the same period (Figure 2).

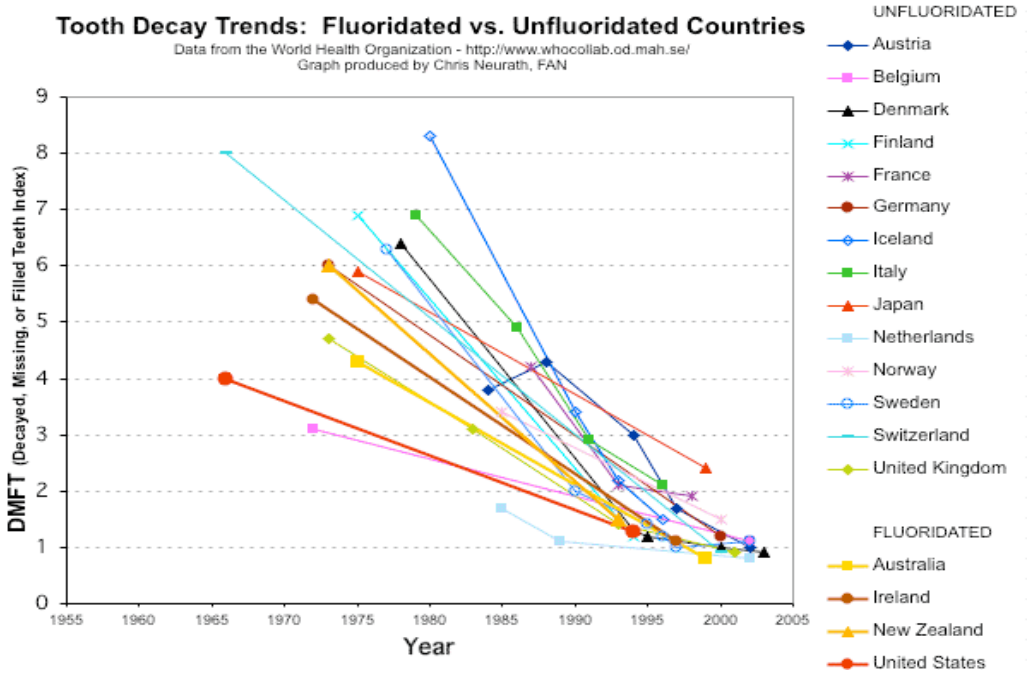


Figure 2. Tooth decay trends among 12-year-olds in fluoridated vs. unfluoridated countries. Source: WHO, http://www.whocollab.od.mah.se/; Graph by Neurath C, FAN.

The evidence that swallowing fluoride actually reduces tooth decay is remarkably weak. In fact, neither the FDA, nor any fluoridation-promoting agency has ever conducted a randomized controlled trial (RCT) to demonstrate efficacy. No longitudinal study reviewed by the York Review (McDonagh et al, 2000) received grade A status. According to this review:

> "…no study used an analysis that would control for the frequency of sugar consumption or the number of erupted teeth per child" (p.24)

When the studies responsible for the launch of fluoridation in the 1940s (e.g. Dean's famous 21-city study, Dean et al., 1942 a,b; and the fluoridation trials, 1945-55) were examined by independent observers such as Ziegelbecker (1981) and Sutton (1998), major weaknesses were described for the methodologies used. The practice of water fluoridation began on very shaky—or even fraudulent—ground. Colquhoun has questioned the honesty of the trial (Hastings versus Napier, 1954-64) that launched fluoridation in New Zealand. The control city of Napier was dropped after one year, and the 60% claimed decreased rate of caries was determined by comparing tooth decay at the beginning and end of the study in the fluoridated community (Hastings) alone, i.e. no comparison with a control (nonfluoridated) group. The 60% decline in caries rate appears to have been an artifact, as the method of diagnosing tooth decay was changed during the course of the trial, an important fact that was not clarified in the final report (Colquhoun, 1997).

According to Colquhoun (1997):

> **"**Before the experiment they had filled (and classified as "decayed") teeth with any small catch on the surface, before it had penetrated the outer enamel layer. After the experiment began, they filled (and classified as "decayed") only teeth with cavities which penetrated the outer enamel layer. It is easy to see why a sudden drop in the numbers of "decayed and filled" teeth occurred. This change in method of diagnosis was not reported in any of the published accounts of the experiment."

The following excerpt from a letter by GN Leslie (1962), Director of the Division of Dental Health in New Zealand, written some 8 years into the trial, reveals that the health authorities were not getting the results that they wanted:

> "No one is more conscious than I am of the need for proof of the value of fluoridation in terms of reduced treatment. It is something that has been concerning me for a long time. It is only a matter of time before I will be asked questions and I must have an answer that have meaning to a layman or I am going to be embarrassed and so is everyone else connected with fluoridation. But it is not easy to get. On the contrary it is proving extremely difficult. Mr. Espie is conferring with Mr. Beck and Mr. Ludwig [Ludwig was the final lead author of the reort, PC] and I am hopeful that in due course they will be able to make a practical suggestion.

> I will certainly not rest easily until a simple method has been devised to prove the equation fluoridation = less fillings." (Letter dated 12 October, 1962)

The whole façade of fluoridation's effectiveness began to crumble in the 1980s, when several authors revealed that there was very little difference in tooth decay between fluoridated and non-fluoridated communities (e.g. Leverett, 1982; Colquhoun 1984, 1985 and 1987; Diesendorf, 1986; Gray, 1987). More recent studies continue to reveal this truth (e.g. de Liefde, 1998; Locker, 1999; and Pizzo et al., 2007).

Furthermore, the largest surveys, in quantitative terms, of tooth decay undertaken in the US (Brunelle and Carlos, 1990) and in Australia (Spencer et al., 1996; Armfield and Spencer, 2004; Armfield et al., 2009 and Armfield, 2010) show very little—if any—difference in tooth decay in the permanent teeth when comparing children who have lived all their lives in a fluoridated community compared to a non-fluoridated one. There are either 4 surfaces to a tooth (the cutting teeth) or 5 surfaces (the chewing teeth). By the time all 24 teeth have erupted there are a total of 128 surfaces. The average difference in these findings of these studies ranges from a saving of 0 to 0.6 of one permanent tooth surface. Thus we are talking about an absolute savings of 0% to <1% of the tooth surfaces in a child's mouth.

Even these small differences would be eliminated if fluoride delayed the eruption of the permanent teeth, for which there is some evidence (Komarek et al., 2005). A one-year delay in tooth eruption would be sufficient to eliminate all the benefits claimed in the studies listed above. When Komarek et al. (2005) allowed for delayed eruption of the permanent teeth, they found no difference in tooth decay in Belgium between children that used F-supplements (designed to deliver about the same dose as a child drinking one liter of water at 1 mg F/L) and those that did not.

The study by Warren et al. (2009), which was part of the multi-million dollar Iowa Fluoride Study funded by U.S. taxpayers, should shake even the most stubborn advocate of water fluoridation. This study was important because it represents the first time an attempt was made to look at tooth decay as a function of how much fluoride children were actually ingesting, rather than the level of fluoride in their water. Here are several quotes from that paper:

> "The 'optimal' intake of fluoride has been widely accepted for decades as between 0.05 and 0.07 mg fluoride per kilogram of body weight (mg F/kg bw), but is based on limited scientific evidence."
>
> "this 'optimal' fluoride intake level is not based on any direct assessment of how such intake relates to the occurrence, or severity, of dental caries and/or dental fluorosis."
>
> "those with fluorosis, either alone or also with caries history, had consistently higher mean fluoride intake levels over the first 4 years of life, whereas the mean

fluoride intakes of those with caries only closely mirrored, but were slightly less than, the intakes of those with neither caries nor fluorosis."

"These findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*, while fluorosis is clearly more dependent on fluoride intake."

"given that most caries prevention is believed to be as a result of topical exposures, it may be of little lesser consequence as to what the 'optimal' fluoride intake level is for caries prevention."

What has become clear is that, while the relationship between fluoride levels in drinking water and dental fluorosis is very robust, the relationship with dental caries is very weak. This is starkly revealed by the figures presented by Iida and Kumar (2009) in a re-examination of the NIDR data from 1986-87, as reported earlier by Brunelle and Carlos (1980). See Table 1, prepared by Thiessen (2011):

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."

In addition to the many studies that have found little difference in tooth decay between fluoridated and non-fluoridated communities, four modern studies—from Finland, British Columbia, former East Germany and Cuba (Künzel et al., 2000a,b; Maupomé et al., 2001; Seppä et al., 2000a,b)—have found that tooth decay did not go up when fluoridation was stopped. One possible explanation as to why there is so little—if any—difference in tooth decay due to ingestion of fluoride, is the universal availability of fluoridated toothpaste. Since the 1980s more and more researchers have indicated that the predominant benefit of fluoride is *topical* not *systemic*. Well over 90% of the toothpaste sold in the US is fluoridated. Even the CDC's Oral Health Division admits that the major benefits are topical, not systemic (CDC, 1999). This admission by the CDC—the primary federal agency promoting fluoridation in the U.S.—should have ended fluoridation there and then. If fluoride works topically, why swallow this substance and expose every tissue to its toxicity? Why accept any risks at all from ingesting fluoride? And why force it on people who don't want it?

Unless the OW can argue convincingly that the studies and conclusions discussed above are without merit, it completely undermines the OW's stated need to protect this program. Thus the OW should abandon the task of developing a RfD and an MCLG that seeks at the same time to protect both the fluoridation program as well as protecting the health of *all* Americans. OW cannot do both. It is the protection of the health of all the American people that the law (SDWA) requires, not the protection of the fluoridation program.

Fluoride certainly does not appear to be doing much good via ingestion, and with the very real potential for harm, as detailed throughout this document, it is puzzling why rational people would continue to push the practice of water fluoridation so aggressively. While the dental community might be reluctant to admit that fluoridation does not live up to the expectations of those who promoted it 60 years ago, there is absolutely no reason today why the EPA's OW should continue to support a practice that may prevent a negligible amount of tooth decay, while putting all other tissues in a child's body at risk for potentially irreparable damage.

### *2.1.2. OW has failed to offer convincing evidence that severe dental fluorosis should be considered the critical effect associated with exposure to fluoride.*

The critical effect is the "adverse effect most likely to occur at the lowest exposure level" (EPA, 2010a, p. 87). OW claims that the proposed RfD for fluoride, as determined for the critical effect of severe dental fluorosis, "is applicable to the entire population since it is also protective for the endpoints of severe fluorosis of primary teeth, skeletal fluorosis and increased risk of bone fracture in adults" (EPA, 2010a, p. 107). OW also claims that "there is no clear evidence that fluoride will cause other types of adverse health effects…at levels as low as those associated with severe dental fluorosis" (2 mg/L; EPA, 2010a, p. 87). OW has failed to offer convincing scientific evidence for either of these assertions.

Biomarkers, as defined by NRC (1989), are "indicators of variation in cellular or biochemical components or processes, structure, or function that are measurable in biological systems or samples." Such biomarkers of exposure to fluoride include concentrations in teeth, bones, nails, hair, urine, blood or plasma, saliva, and breast milk (ATSDR, 2003; NRC, 2006). NRC (2006, p. 79) states that "The two most important biomarkers of effect for fluoride are considered to be enamel fluorosis and skeletal fluorosis (ATSDR, 2003)." However, several altered physiological states have been observed to coincide with severe dental fluorosis (e.g. reduced levels of T4, calcium, and sodium; increased QT and QTc intervals; Olgar et al., 2009), and numerous studies point to potentially adverse effects at levels of fluoride exposure far below that associated with severe dental fluorosis.

For example, several endocrine effects have been observed at fluoride doses at or below that being proposed by OW as the new RfD. These include altered thyroid function (T4 and T3 concentrations) and elevated TSH concentrations at 0.05-0.1 mg/kg/day (0.03

mg/kg/day with iodine deficiency); elevated calcitonin concentrations at 0.06-0.87 mg/kg/day; goiter prevalence >20% at 0.07-0.13 mg/kg/day (≥0.01 mg/kg/day with iodine deficiency); and impaired glucose tolerance at 0.07-0.4 mg/kg/day (NRC, 2006).

Parameters of kidney function have also been found to be altered at levels within the range of that proposed by OW as the new RfD. For example, the amount of plasma membrane and endoplasmic reticulum $Ca^{++}$-pump protein in kidney membranes of rats showed a significant reduction associated with a plasma concentration of only 2 umol F/L (Borke and Whitford, 1999). This level is equivalent to that achieved in humans with an intake of perhaps 2.2 mg F/day (Teotia et al., 1978; NRC, 2006, p. 70), or 0.03 mg/kg/day for a 70 kg adult.

Development of severe dental fluorosis is only an issue for the first 8 years or so of a child's life, as it cannot occur after the permanent teeth have erupted. On the other hand, the risks of stage II skeletal fluorosis and bone fractures (particularly hip fractures) are a lifelong concern. A dose of fluoride that was insufficient to cause severe dental fluorosis in a child—if consumed on a daily basis for the rest of a person's life—might well induce permanent changes in the bones. Moreover, while an uncertainty factor of one—in our view—is not sufficient to protect against severe dental fluorosis, it most certainly is not sufficient in the case of skeletal fluorosis or bone fractures.

Fluoride accumulates in the body over a lifetime, with some authors noting that 99% of retained fluoride is found in bones and teeth (Hamilton, 1990; Kaminsky et al., 1990; WHO, 2002). Young bones are more receptive to fluoride accumulation than are older bones (Whitford, 1999), as evidenced by the greater percentage of fluoride retained by infants than by adults (Ekstrand et al, 1994). Thus, the developing skeletal system of children is likely to be more sensitive to fluoride exposure than is that of an adult. As the proportion of retained fluoride in teeth is substantially less than that retained in bone (Ayoob and Gupta, 2006), it is likely that any effects of fluoride on the developing teeth—even mild or very mild dental fluorosis—are indicators of even greater changes to the developing bones.

Several studies indicate that bone damage or bone changes may occur prior to the development of severe dental fluorosis. Research from India, where most data relating to endemic fluorosis has been generated, has found skeletal fluorosis associated with water fluoride levels of 2-3 mg/L, and as low as 0.7 mg/L (Ayoob and Gupta, 2006). The prevalence of skeletal fluorosis was found to be between 2-8% for populations with water fluoride levels at 1.4 mg/L (Jolly, 1968; Choubisa et al., 1997, 2001; Xu et al., 1997). The Chinese government now considers any water supply containing over 1 ppm fluoride a risk for skeletal fluorosis (Bo et al., 2003). In one study, 9 of 14 villages in India had a rate of skeletal fluorosis that was at least twice that of the rate of dental fluorosis (Susheela, 2003), providing sound evidence that dental fluorosis is not always a more sensitive indicator of fluoride over-exposure. NRC (2006) indicates a lack of information on the prevalence of stage II skeletal fluorosis in the U.S., with very few reports of stage II and stage III skeletal fluorosis being reported. However, lack of evidence of harm does not indicate lack of harm, and NRC (2006) recommended that more research be

conducted. Presently, there are several studies that should be considered more thoroughly concerning bone changes in response to fluoride intake.
Concerning "optimally" fluoridated water supplies, Schlesinger et al. (1956) found a statistically significant doubling of cortical bone defects in the children in fluoridated Newburgh compared to non-fluoridated Kingston (12.5% versus 7.5%). The cortical bone is the lamellar structure on the outside layer of the bone, which protects against non-compressive fractures. Ironically, even though this observation was ignored as far as pursuing the issue of bone fractures among children in fluoridated communities was concerned, it was the eventual starting point for the possibility that fluoride might cause osteosarcoma in young males. According to Dr. Caffey who examined the bone X-rays, the anatomical, gender and age distribution of these defects was remarkably similar to the same distributions in osteogenic sarcoma (another name for osteosarcoma) (NRC, 1977; Connett P, et al., 2010, Ch.18). Despite the present of these bone defects, no cases of severe dental fluorosis were observed in the fluoridated community, indicating that cortical bone defects may be more sensitive to fluoride exposure than dental fluorosis.

A study of children and adults in Mexico (Alarcon-Herrera, et al., 2001) found a direct linear association between the severity of dental fluorosis and bone fractures in both children and adults. This very striking finding indicates that fractures doubled between those with no dental fluorosis and those with very mild dental fluorosis, and doubled again between those with very mild dental fluorosis and mild dental fluorosis. Clearly, such a finding negates any notion that weakening of bones will occur only after fluoride exposures have reached the point of causing severe dental fluorosis. It is interesting that no fluoridating country (including the U.S.) has ever sought to reproduce this study, nor for that matter—except for one small study by Morgan et al. (1998)—have they used the very obvious biomarker of the severity of dental fluorosis in epidemiological studies to probe fluoride's possible relationship with various other ailments.

OW sets considerable store by the important bone study of Li et al. (2001), but uses the study selectively and fails to identify problems with the data analysis, thereby potentially underestimating the risk fluoride poses to hip fracture in the elderly. A more critical analysis of the Li data would suggest an RfD lower than that proposed for severe dental fluorosis. The Li et al. (2001) study reported bone fractures in six Chinese villages in which the well water increased from less than 0.3 ppm to greater than 4 ppm. The authors reported (a) on the prevalence of ALL fractures and also (b) on HIP fractures only. Both the NRC (2006) and OW rate this as a strong and important study. The OW, while tabulating the results of the whole study, concentrates selectively on the total fractures, for which they provide only graphical data. These data suggested a U-shaped curve, where the fractures in the two villages with water <1 ppm (villages 1 and 2) were higher than the village at 1 ppm (village 3), but the fracture rate for villages 4, 5 and 6 increased in what looks like a linear fashion. This part of the study has been offered by some fluoridation promoters as evidence that fluoride is actually protective of bone fractures at or around 1 ppm. However, it should be noted that the apparent U-shape is much less evident and not statistically significant when data for total fractures in people over 50 years of age are considered.

It is not understood why Li et al. (2001) did not plot the fracture data on a proper numerical scale. Data were available to do not only that, but also to plot fractures against estimates of fluoride consumption, rather than merely fluoride concentration in water. Their plots have proved misleading to readers, including the OW. Figures 3 and 4 re-plot the fracture data against water consumption using data from Li et al. (2001), summarized in Tables 1 and 2.

| Village | Water F (ppm) | Average Daily Intake (mg/day) | Number Surveyed | Number of All Fractures | Prevalence (%) |
|---|---|---|---|---|---|
| 1 | 0.25 – 0.34 | 0.73 | 1,363 | 101 | 7.41 |
| 2 | 0.58 – 0.73 | 1.62 | 1,407 | 90 | 6.40 |
| 3 | 1.00 – 1.06 | 3.37 | 1,370 | 70 | 5.11 |
| 4 | 1.45 – 2.19 | 6.54 | 1,574 | 95 | 6.04 |
| 5 | 2.62 – 3.56 | 7.85 | 1,051 | 64 | 6.09 |
| 6 | 4.32 – 7.97 | 14.13 | 1,501 | 111 | 7.40 |

Table 1. All fractures (since the age of 20 years) in six Chinese villages with average fluoride intakes varying from 0.7 to 14 mg/day. Source: Li et al., 2001.

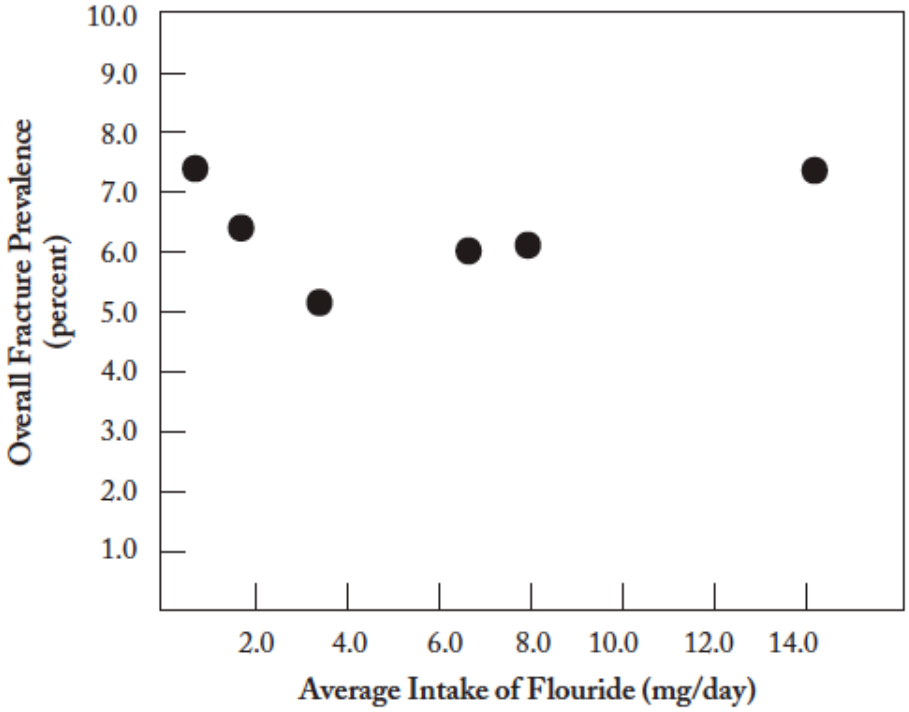


Figure 3. Prevalence of all bone fractures (since the age of 20 years) plotted against average daily fluoride intakes in six Chinese populations; data from Li et al. (2001), summarized in Table 1.

| Village | Water F (ppm) | Average Daily Intake (mg/day) | Number Surveyed | Number of Hip Fractures | Prevalence (%) |
|---|---|---|---|---|---|
| 1 | 0.25 – 0.34 | 0.73 | 1,363 | 5 | 0.37 |
| 2 | 0.58 – 0.73 | 1.62 | 1,407 | 6 | 0.43 |
| 3 | 1.00 – 1.06 | 3.37 | 1,370 | 5 | 0.37 |
| 4 | 1.45 – 2.19 | 6.54 | 1,574 | 14 | 0.89 |
| 5 | 2.62 – 3.56 | 7.85 | 1,051 | 8 | 0.76 |
| 6 | 4.32 – 7.97 | 14.13 | 1,501 | 18 | 1.20 |

Table 2. Hip fracture rates (since the age of 20 years) in six Chinese villages with average fluoride intakes varying from 0.7 to 14 mg/day. Source: Li et al., 2001.

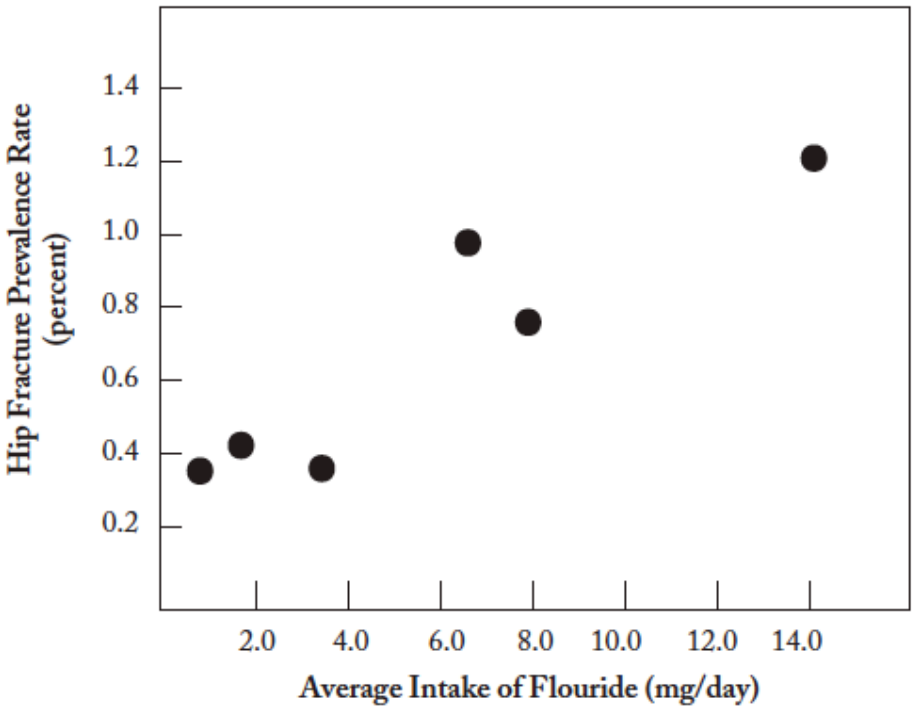


Figure 4. Prevalence of hip fractures (since the age of twenty years) plotted against average daily fluoride intakes in six Chinese populations; data from Li et al. (2001), summarized in Table 2.

The hip data (Figure 4) now look consistent with a *simple straight line relationship*

*between fracture frequency and fluoride consumption*. A very similar relationship is seen when plotting against water fluoride concentration (plot not shown). This more orthodox presentation of what are generally considered the strongest available data puts into serious question whether there is *any threshold at all* for the fluoride effect on hip fracture. Based on the linear trend illustrated in Figure 4, hip fractures may increase at doses of 3 mg/day or even lower, and certainly at levels lower than the RfD of 5.6 mg/day (0.08 mg/kg/day) developed by OW for the end point of severe dental fluorosis.

Levy et al. (2009) observed fluoride intakes recorded from birth and compared them with bone measurements taken in children at 11 years old. Fluoride intake was significantly correlated with several bone measures, including hip and spine BMC (bone mineral content) and spine BMD (bone mineral density) in girls; hip, spine, and whole-body BMC and spine BMC in boys. When corrected for age, height, weight and Tanner stage, no significance was determined ($p<0.01$). However, consistent trends were observed. For girls, there was a negative trend for regression coefficients at all age groupings for hip and whole-body BMC, hip and spine BMD, and at two age groupings for spine BMC. For boys, there was a positive trend for regression coefficients for all measurements at all age groupings. Despite the authors' insistence that the lack of significant findings provides "no evidence that fluoride intakes have consequences for bone outcomes at age 11 years in girls or boys within these ranges (0.54-0.81 mg F/day; 0.12-0.18 mg/kg/day for average body weights 44-45 kg), it is important to remember the accumulative nature of fluoride in bones. These consistent trends—while perhaps not capable of reaching significance at the p-value ($p<0.01$) chosen for this study—are indicative of the onset of lifelong alterations in bone structure that will not be reversed as long as intakes of fluoride, even at the relatively low levels observed in this study, are continued. Thus the trend for increased BMC and BMD found in boys may be representative of the earliest pre-clinical stages of skeletal fluorosis (NRC, 2006), while the trend for decreasing BMC and BMD found in girls may be indicative of very early onset of osteoporosis, indicated by some authors to be aggravated by fluoride, even at relatively low levels (Krishnamachari, 1986; Jacobson et al., 1990; Cooper et al., 1991; Danielson et al., 1992; Kleerekoper, 1994).

Perhaps equally important is that the types of bones affected for girls in the Levy et al. (2009) show the same patterns in this study as have consistently been observed in clinical trials—i.e. density of the trabecular-rich axial skeleton (spine) is slightly increased (albeit not significantly), while the cortical-rich appendicular bone (hip) was decreased (often significantly). This is potentially quite significant since fluoride's differential effect on bone density has been considered a causative factor in the appendicular fractures (e.g. hip fractures) consistently observed in other studies. In other words, if low-level fluoride is capable of causing a differential effect on bone density, it means that low-level fluoride can reduce the integrity of cortical bone. This, in fact, is consistent with Phipps' (2000) finding of increased wrist fractures (wrists are almost entirely comprised of cortical bone), as well as the other epidemiological findings of increased hip fractures (since the strength of the hip is primarily dependent on cortical bone).

Also worth mentioning here is that the children included in the Levy et al. (2009) study

were mostly White, of higher socioeconomic status (SES), and with relatively low fluoride intakes (Levy et al., 2009). However, as discussed in Sections 2.1.4. and 2.5.4., certain minority groups and people of lower SES have statistically greater intakes of fluoride, and increased rates of dental fluorosis (including the more severe forms) than do Whites or people of higher SES (Beltrán-Aguilar et al., 2005). It would be interesting to determine similar bone measurements for these groups, as it is possible that more extreme morphological alterations would be revealed in response to chronic fluoride intakes.

Chachra et al. (2010) compared the fluoride content and mechanical properties of bone specimens from citizens of either Montreal (non-fluoridated) or Toronto (fluoridated). The strength of the hip bones decreased as the fluoride content increased, a finding that the authors acknowledge is "consistent with some previous animal studies." While age may possibly explain this finding (since the older a bone is, the higher its F content will be), the authors did not verify this one way or the other. Thus, as it stands, the study should serve as a major red flag, especially given that the patients in the study had only been exposed to fluoridation for about 30 years.

While a great deal of the focus on the studies that have been performed in fluoridated countries has been on the bone itself, it should not be forgotten that the first symptoms of skeletal fluorosis (e.g. stiffness and pains in the joints) may have more to do with fluoride's interaction with the connective tissue, than with the bone itself. Joint pain and stiffness have been reported by people who claim to be sensitive to fluoridated water at 1 ppm (Waldbott, 1998, post.). In Indian villages one of the ways villagers are tested for the early stages of skeletal fluorosis is to see if they can touch their chest with their chin, or if they can reach back and touch their fingers behind their necks (Chinoy, 2000).

The proposed RfD of 0.08 mg F/kg/day is based on IOM's (1997) recommended AI for fluoride (0.05 mg/kg/day) for all persons $\geq$6 months. The decision that only doses above this level would be considered as points of departure for the drinking water component of an oral RfD analysis, means that OW selectively eliminated from consideration any doses less than 0.05 mg/kg/day as the threshold dose for severe dental fluorosis (EPA, 2010a, p. xv). This elimination of data was not based on evidence of lack of harm from dental fluorosis, nor was it based on lack of harm from other endpoints, as indicated above.

In addition, by using only severe dental fluorosis as the endpoint of concern, OW is failing to protect America's teenagers from the likely psychological damage caused by moderate dental fluorosis. According to H. Trendley Dean (the "father" of water fluoridation), moderate dental fluorosis discolors and disfigures 100% of the tooth enamel. Moderate and severe dental fluorosis combined currently impacts 3.6% of all American children aged 12-15 (Beltrán-Aguilar et al., 2010). NRC (2006) states "the committee finds that it is reasonable to assume that some individuals will find moderate enamel fluorosis on front teeth to be detrimental to their appearance and that it could affect their overall sense of well-being." (p. 5). According to NRC (2006), "only 24.2% of parents were satisfied with the color of their children's teeth when the TSIF score was 4 or greater (moderate or severe dental fluorosis), versus. 73.9% satisfaction with not dental fluorosis." An ad-hoc panel of behavioral scientists convened by the U.S. EPA

and the National Institute of Mental Health in 1984 to evaluate the psychological impacts of fluorosis concluded that "individuals who have suffered impaired dental appearance as a result of moderate and severe fluorosis are probably at increased risk for psychological and behavioral problems or difficulties" (Kleck RE, cited in 50 FR 20164, EPA, 1985; NRC, 2006, p. 119).

*2.1.3. OW has failed to consider potential variation in responses to the different types of fluoride in drinking water.*

The physio-chemical properties of naturally occurring sources of fluoride, pharmaceutical grade sodium/stannous fluoride, and the industrial grade silicofluorides (as used in artificial water fluoridation) are distinct, yet OW has not taken these differences into consideration in its dose-response analysis. Approximately 75% of artificially fluoridating water systems, accounting for 90% of the people served, employ fluosilicic acid or sodium fluosilicate (i.e. fluorosilicates or silicofluorides) to raise the level of fluoride in drinking water to the recommended "optimal" level to "protect against dental caries" (NRC, 2006). Silicofluorides are a by-product from the manufacture of phosphate fertilizers (NRC, 2006, p. 15; Haneke and Carson, 2001). In fact, according to Thomas Reeves, former National Fluoridation Engineer for the CDC's Oral Health Division, "All of the fluoride chemicals used in the U.S. for water fluoridation, sodium fluoride, sodium fluorosilicate, and fluorosilicic acid, are byproducts of the phosphate fertilizer industry" (Reeves, 2000).

Despite claims that the "standard toxicity database for fluoride is complete" (EPA, 2010a, p. 106), that of silicofluorides is sparse, and "essentially no studies have compared the toxicity of Silicofluorides with that of sodium fluoride" (NRC, 2006, p. 53). EPA has admitted that it has no "empirical scientific data on the effects of fluosilicic acid or sodium silicofluoride on health and behavior" (Thurnau, EPA NRMRL, 2000). NRC (2006, p. 223) states "Most of the studies dealing with neural and behavioral responses have tested NaF. It is important to determine whether other forms of fluoride (e.g. silicofluorides) produce the same effects in animal models."

A few studies that have looked at silicofluorides have found an association between exposure to silicofluorides in water and increased blood lead levels in children (Masters and Coplan, 1999; Masters et al., 2000). The four different human leukemic cell lines have been found to be more susceptible to the effects of sodium hexafluorosilicate than to NaF (Machalinski et al., 2003). NRC (2006) recommended that "Further research is needed to elucidate how fluorosilicates might have different biological effects from fluoride salts" (p. 221).

The assumption that silicofluorides completely dissociate in water (Urbansky and Schock, 2000) has been questioned (Coplan and Masters, 2001). The possibility that intermediate species (e.g. $SiF_5^{1-}$) exist under acidic conditions has been indicated (Urbansky, 2002; Morris, 2004; NRC, 2006, p. 53). Also possible is that SiF residues re-associate within the stomach (intra-gastric pH levels ~2.0; Ciavatta et al., 1988) and

during food preparation, producing SiF-related species such as silicon tetrafluoride, a known toxin (Coplan, 2002).

Hexafluorosilicic acid and sodium hexafluorosilicate were nominated in 2002 for review by the National Toxicology Program (NTP) for chemical and toxicological characterization (including chronic toxicity, carcinogenicity, neurotoxicity, and toxicokinetics), and mechanistic studies related to cholinesterase inhibition and lead bioavailability (NTP, 2002).

Sodium hexafluorosilicate and fluorosilicic acid are both listed in Section 8(b) of the Toxic Substances Control Act, and EPA has referred to the "high inherent toxicity" of sodium hexafluorosilicate (EPA, 1999). In addition, fluorosilicic acid can contain any number of other contaminants. These include heavy metals such as arsenic (Hazan, 2000; Weng et al., 2000) and lead (Hazan, 2000), and radioactive elements such as uranium (Guidry et al., 1986; IAEA, 1989; WISE online), radium-226, radium-222, polonium-210 and lead-210 (Guidry et al., 1986).

After dilution of the hexafluorosilicic acid, the level of arsenic in the public water supply can reach 1 ppb (Weng et al, 2000). Such a level exceeds the MCLG for arsenic of zero. 1 ppb arsenic carries an incremental cancer risk for lifelong exposure of 1 in 1000, which would normally be an unacceptable risk for any project seeking approval from the EPA. While it is understandable that the MCL for arsenic should be set higher than zero because of the very high economic costs or removing natural arsenic down to this level, this should not be used as an excuse for knowingly exceeding the MCLG by deliberately adding arsenic contaminated fluoridating agents to the drinking water. Should the OW be able to providing convincing evidence that a) fluoridation reduces tooth decay by a significant extent and b) poses no other unacceptable risks such as lowered IQ in children, then at the very least it should insist that only pharmaceutical grade fluoridating agents be used for this purpose.

As per Haneke and Carson (2001), no data were available at that time concerning short-term/subchronic exposure, chronic exposure, cytotoxicity, reproductive/teratological effects, or carcinogenicity of sodium hexafluorosilicate or fluorosilicic acid. To our knowledge, no new data on the long-term safety of silicofluorides have come available.

*2.1.4. Despite numerous uncertainties inherent in its analysis, OW has failed to apply appropriate safety factors.*

OW's abandoning normal safety factors in deriving an RfD for severe dental fluorosis is unacceptable. OW admits that its analysis is riddled with uncertainties: "Various physiological factors, such as calcium deficiency, co-exposure to certain minerals, malnutrition, respiratory or metabolic acidosis or alkalosis, and various pathological conditions affecting urinary output and kidney function, may contribute to increases in the prevalence and severity of dental fluorosis...which may, in part, account for reports of high levels of fluorosis in some populations exposed to low levels of fluoride. These

factors introduce an unquantifiable degree of uncertainty in interpreting dose-response data for fluoride-induced dental fluorosis" (EPA, 2010a, p. 36). Yet, OW continues to tout the presumed benefits of fluoride in order to avoid dealing with these uncertainties in a traditional manner—i.e. by incorporating uncertainty factors into its calculations.

Specifically, applying an uncertainty factor of 1 (i.e. applying no margin of safety) when extrapolating from a 70 year-old study (Dean, 1942) to an RfD designed to protect the whole U.S. population today is unjustifiable. OW acknowledges a number of weaknesses in Dean's data (EPA, 2010a, pp. 12-13), including a serious lack of data concerning: occurrence of dental caries; potential confounding factors (e.g. unique dietary fluoride intakes); drinking water intakes; differences in dental hygiene, dietary intakes, body weights, and puberty/hormonal condition; and differences in racial or ethnic susceptibility (i.e. only white children were included in Dean's study). For the data that were available, no statistical analysis was employed.

It is precisely because vulnerabilities to toxic substances vary so widely across a human population that a safety factor is applied to the LOAEL (lowest observable adverse effect level) in deriving an RfD; a dose supposedly safe for everyone. This safety factor is sometimes called an "uncertainty factor," and Dean's data clearly contains much uncertainty as far as extrapolating to the whole population is concerned. Factors that can affect vulnerabilities to toxic substances such as fluoride include racial and ethnic differences, age, nutritional and health status, income, and level of education. The only way that OW could take into account the deficiencies in Dean's data to adequately account for the full range of vulnerability is to apply an appropriate uncertainty factor. However the OW has applied NO uncertainty factor to Dean's data, and thus has undermined the credibility of its whole exercise.

OW is also in violation of the SDWA, which states that an adequate margin of safety must be applied. According to SWDA:

"Each maximum contaminant level goal . . . shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and *which allows an adequate margin of safety*." (our emphasis)

OW defends the use of an uncertainty factor 1 as follows:

> In establishing an estimated oral RfD for fluoride, data on nutritional benefit were assessed in combination with the data on severe dental fluorosis to define a level that provides anticaries protection without causing severe dental fluorosis when consumed daily for a lifetime. Conventional application of uncertainty factors is not always appropriate when carrying out a risk assessment for nutrients and other beneficial substances, especially when there is a relatively small difference between the levels that satisfy need and those that cause adverse effects. For this reason the total uncertainty factor applied was 1. (EPA, 2010a, p. 105)

By using a safety factor of 1, OW is claiming that the full range of sensitivity to fluoride

among the American population in 2011—with its vast spectrum of racial, ethnic, and socioeconomic—was completely accounted for by a study of approx 5000 children in the 1930s. This is quickly countered by the fact that all children in the Dean (1942) study were white. However, numerous studies indicate that black children are more susceptible to dental fluorosis (and probably other harmful effects of fluoride) than are white children. Using an uncertainty factor of 1 here is tantamount to perpetrating environmental injustice against black children.

The National Research Council 1993 Review (NRC, 1993) reported four earlier studies showing that ethnicity plays a role in the effects of fluoride:

- Russell (1962), in the Grand Rapids fluoridation study, noted that fluorosis was twice as prevalent among African-American children as white children.
- In the Texas surveys in the 1980s, the odds ratio for African-American children having dental fluorosis, compared with Hispanic and non-Hispanic white children, was 2.3 (Butler et al., 1985).
- Dental fluorosis also tended to be more severe among African-American children than white children in the Georgia study (Williams and Zwemer, 1990), although the difference was not statistically significant.
- In Kenya, prevalence and number of severe cases were unexpectedly high when related to fluoride concentrations in drinking water (Manji et al., 1986), although nutritional factors could have confounded these results. The reasons for these findings are unknown and do not seem to have been explored further.

Data published in CDC's Morbidity and Mortality Weekly Report in 2005 (Beltrán-Aguilar et al., 2005) show that Black and Mexican Americans have significantly higher levels of the worst forms of dental fluorosis than do Whites, as shown in Table 1.

| | Unaffected | | Questionable | | Very mild | | Mild | | Moderate/Severe | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | %† | SE§ | % | SE | % | SE | % | SE | % | SE |
| **Age group (yrs)** | | | | | | | | | | |
| 6–11 | 59.81 | 4.07 | 11.80 | 2.50 | 19.85 | 2.12 | 5.83 | 0.73 | 2.71 | 0.59 |
| 12–15 | 51.46 | 3.51 | 11.96 | 1.84 | 25.33 | 1.98 | 7.68 | 0.93 | 3.56 | 0.59 |
| 16–19 | 58.32 | 3.30 | 10.21 | 1.70 | 20.79 | 1.78 | 6.65 | 0.67 | 4.03 | 0.77 |
| 20–39 | 74.86 | 2.28 | 8.83 | 1.23 | 11.15 | 1.22 | 3.34 | 0.58 | 1.81 | 0.39 |
| **Sex** | | | | | | | | | | |
| Male | 67.65 | 2.63 | 9.99 | 1.45 | 15.65 | 1.52 | 4.58 | 0.54 | 2.12 | 0.39 |
| Female | 66.97 | 2.84 | 9.83 | 1.34 | 15.58 | 1.36 | 4.84 | 0.61 | 2.78 | 0.49 |
| **Race/Ethnicity¶** | | | | | | | | | | |
| White, non-Hispanic | 69.69 | 3.13 | 10.43 | 1.62 | 14.09 | 1.56 | 3.87 | 0.60 | 1.92 | 0.48 |
| Black, non-Hispanic | 56.72 | 3.30 | 10.40 | 2.16 | 21.21 | 2.16 | 8.24 | 0.82 | 3.43 | 0.54 |
| Mexican-American | 65.25 | 3.89 | 8.95 | 1.29 | 15.93 | 2.24 | 5.05 | 0.72 | 4.82** | 1.81 |
| **Poverty status††** | | | | | | | | | | |
| <100% FPL | 68.02 | 3.21 | 10.67 | 1.64 | 14.28 | 1.73 | 4.07 | 0.69 | 2.97 | 0.66 |
| 100%–199% FPL | 66.92 | 2.91 | 9.11 | 1.79 | 16.11 | 1.46 | 5.21 | 0.78 | 2.65 | 0.56 |
| ≥200% FPL | 66.88 | 2.75 | 10.73 | 1.33 | 15.56 | 1.56 | 4.83 | 0.50 | 2.00 | 0.37 |
| **Total** | **67.40** | **2.65** | **9.91** | **1.35** | **15.55** | **1.37** | **4.69** | **0.49** | **2.45** | **0.40** |

* Using Dean's index. All estimates are adjusted by age (single years) and sex to the U.S. 2000 standard population, except sex, which is adjusted only by age.
† Weighted prevalence estimates.
§ Standard error.
¶ Calculated using "other race/ethnicity" and "other Hispanic" in the denominator.
** Unreliable estimate: the standard error is 30% the value of the point estimate, or greater.
†† Percentage of the Federal Poverty Level (FPL), which varies by income and number of persons living in the household.

Table 1. Enamel fluorosis* among persons aged 6-39 years, by selected characteristics—

United States, National Health and Nutrition Examination Survey, 1999-2002. Source: Beltrán-Aguilar et al., 2005.

While EPA acknowledges the results of a study by Sohn et al. (2001) that "Fluid intake was significantly associated with age, sex, socioeconomic status, and race and ethnicity," EPA failed to include this association in its risk assessment. Sohn et al. (2001) states "The effect of race or ethnicity and socioeconomic status (SES) on fluid consumption were particularly noticeable," with African American children consuming significantly more plain water and less milk than other racial or ethnic groups (white children consumed the least amount of total fluid and plain water), and children from the low SES group consuming significantly more plain water and less milk than higher SES groups.

A paper in the 2009 *Journal of Public Health Dentistry* reviewed the available research and concluded that "African-American children, and/or children of lower SES, are ingesting significantly more fluoride than children who are higher on the social scale. They may be therefore at higher risk for fluorosis." (Sohn et al., 2009)

There may be several reasons why black children are more susceptible to developing dental fluorosis than white children. In addition to ingesting more fluoride (as indicated above) it may also reflect dietary differences. Some black children are lactose intolerant and therefore have less protective calcium and less vitamin D in their diets. Dark pigmentation reduces the synthesis of Vitamin D in the skin at a given level of sunlight, and reduction of sunlight by inner-city pollution may be a further factor. Another possible association was raised by Leite et al. (2011). In this study the authors found that rats treated with both lead and fluoride had worse dental fluorosis than rats treated with fluoride alone. Thus it is possible that children from inner city areas that have already been compromised with lead exposure will be more susceptible to developing dental fluorosis.

One can only assume that OW has not recognized the lack of Environmental Justice inherent in its use of an uncertainty factor of 1. However, whether it realizes it or not, in developing this RfD in this manner OW has simply failed to protect a vulnerable minority in the population. This is clearly in violation of a U.S. Executive Order (12898, 1994) and one of the stated goals of EPA administrator Lisa Jackson (EPA, 2011a).

Another aspect of water fluoridation that impinges on Environmental Justice is that the children traditionally targeted for water fluoridation (with the best of intentions) have been from low-income families, which are a) least able to avoid fluoridated water if they don't want to drink it; b) more likely to suffer nutritional deficiencies because of poor diets, and therefore are more prone to the toxic effects of fluoride; and c) are least likely to be able to afford restorative dental work for dental fluorosis, a condition from which they are more likely to suffer (Beltrán-Aguilar et al., 2005; Table 1). Even if the proposed RfD for severe dental fluorosis is valid, the notion that even 0.5% of Americans—roughly 155,000 people—will have to endure this horrible life-long condition, is unacceptable. That minorities and people of low socioeconomic status are at an increased risk for falling victim to this condition is nothing short of criminal.

Nearly every State Oral Health report indicates that minority children and children from low-income families have higher rates of dental caries. Only two out of the 67 State Oral Health reports reviewed in 2010 (Connett E, 2010) included rates of dental fluorosis (i.e. California, 1993-94, which was not performed by a State agency; and Utah, 2005). As every State report recommended fluoridation of the drinking water to reduce caries, it should be of concern that the inclusion of statistics on dental fluorosis are not being recommended, despite the increasing prevalence of dental fluorosis in the United States (nearly 41% for adolescents 12-15 years-old; Beltrán-Aguilar et al., 2010).

In a summary document, OW declares that the proposed RfD is based only on the "critical health effect of pitting of the enamel in severe dental fluorosis," and that "Additional research will be necessary to obtain dose-response data amenable to a quantitative risk assessment for State II skeletal fluorosis and/or skeletal fractures" (EPA, 2011, 822-F-11-001). Yet the assertion is made in the Dose-Response Analysis that the RfD estimate of 0.08 mg F/kg/day "is an estimate of the fluoride dose that will protect against severe dental fluorosis, clinical stage II skeletal fluorosis and skeletal fractures" (EPA, 2010a, p. ii). It is even repeatedly claimed that this RfD will be protective against severe dental fluorosis of the primary teeth (EPA, 2010a), despite that OW could not possibly have scientific evidence of this, as it has ignored fetuses and infants <6 months in its analysis.

The proposed RfD for severe dental fluorosis, even if valid for that endpoint, wouldn't necessarily protect against Stage II skeletal fluorosis, bone fractures, or any of the other numerous adverse effects that have been documented in the scientific literature (NRC, 2006; Connett P, et al., 2010). Each of these end points requires its own RfD with appropriate uncertainties applied to the data in each case. OW is threatening the health of the American people by determining a single RfD for fluoride a) based solely on the endpoint of severe dental fluorosis, and b) which includes *absolutely no margin of safety*.

It is clear from the above that the OW's reason given for not using the normal safety factor of 10 to allow for intra-species variation is not scientifically based, but politically based. It emphasizes OW's objective of protecting the water fluoridation program over protecting the health of the population.

*2.2. OW has unnecessarily delayed consideration of the potential carcinogenicity of fluoride.*

The OW should not delay any further a weight of evidence analysis of fluoride's potential to cause osteosarcoma (a frequently fatal bone cancer) in boys and young men (Bassin et al., 2006). Such an analysis is likely to show that fluoride meets the EPA's description of a chemical that is "Likely to be carcinogenic to humans" and thus force an MCLG of zero. We expect the EPA has delayed this analysis in the hope that a paper promised by Chester Douglass (Bassin's thesis advisor) for the Summer of 2006 would negate Bassin's findings, but that paper is long overdue (by nearly 5 years) and the methodology used is not capable of refuting Bassin's central finding (Neurath and Connett, 2008). Furthermore, the NRC (2006) evaluation of Bassin's work was based on her unpublished PhD dissertation. The NRC panel indicated that "more weight would be given to an assessment of fluoride as a human carcinogen" (NRC, 2006, p. 329) with peer-reviewed publication of these findings.

The EPA may have put itself and this country through a great deal of unnecessary extra work by failing to start with an analysis of whether the weight of evidence favors classifying fluoride as a known or probable human carcinogen. Such a finding would have forced setting the MCLG for fluoride at zero, like lead and arsenic, because according to the EPA there are no safe levels for human carcinogens.

In reference to the potential of fluoride to promote cancer, NRC wrote in 2006:

> Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed (Tables 10-4 and 10-5). As noted above, osteosarcoma is of particular concern as a potential effect of fluoride because of (1) fluoride deposition in bone, (2) the mitogenic effect of fluoride on bone cells, (3) animal results described above, and (4) pre-1993 publication of some positive, as well as negative, epidemiologic reports on associations of fluoride exposure with osteosarcoma risk. (p. 336)

In 2001, Else Bassin, a graduate student at the Harvard Dental School, successfully defended her doctoral thesis, which included a case-control study that found young boys were at a 5- to 7-fold increased risk for developing osteosarcoma by the age of 20 when exposed to fluoridated water between 6 and 8 years of age (Bassin, 2001).

In response to the study by Bassin, NRC (2006) stated:

> A unique feature of the analysis published in the literature so far was an exploratory analysis of ORs (odds ratios) for each specific year of age. Bassin found elevated ORs for the highest tertile compared with the lowest centering on ages 6 to 8. At age 7, the respective ORs (and 95% confidence intervals) were 7.2 (1.7 to 30.0) for males and 2.0 (0.43 to 9.28) for females. For the highest tertile, graphed results for males indicated a gradual increase and then a decrease of

> estimated relative risk from exposure at ages 0 to 15 with peaks at age 7, with the middle tertile, compared with the lowest, showing stable ORs across all ages…
>
> …the highest ORs at ages 6 to 8, during what the author describes as the "mid-childhood growth spurt for boys," are consistent with some previous ecologic or semiecologic studies (Hoover et al. 1991; Cohn 1992) and with a hypothesis of fluoride as an osteosarcoma risk factor operating during these ages. A publication based on the Bassin thesis is expected in the spring/summer of 2006 (E. Bassin, personal communication, Jan. 5, 2006). If this paper provides adequate documentation and analyses or the findings are confirmed by another study, more weight would be given to an assessment of fluoride as a human carcinogen. (p. 329)

NRC (2006) also commented on a related study conducted by Bassin's thesis adviser, Chester Douglass:

> A relatively large hospital-based case-control study of osteosarcoma and fluoride exposure is under way (Douglass, 2004) and is expected to be reported in the summer of 2006 (C. Douglass, Harvard School of Dental Medicine, personal communication, January 3, 2006). (p. 329)
>
> The results of the Douglass et al. multicenter osteosarcoma study (expected in the summer of 2006) could add important data to the current body of literature on fluoride risks for osteosarcoma because the study includes bone fluoride concentrations for cases and controls. When this study is published, it should be considered in context with the existing body of evidence to help determine what follow-up studies are needed. (p. 338)

In the nearly 5 years since the NRC made these observations, Bassin has published her research (Bassin et al., 2006). Within the same issue of the journal that Bassin's research was published, Douglass included a letter repeating his claim that his related study would not support Bassin's findings (Douglass and Joshipura, 2006). Although promoters of fluoridation in several countries have used this unpublished, and un-peer-reviewed claim to deflect attention from Bassin's finding (sometimes giving the impression that Douglass's claim in the letter to *Cancer Causes and Control* was actually a published study), as of April 2011, the Douglass study has still not been published.

Moreover, examination of the methodology described by Douglass indicates that it is highly unlikely that findings from this research could discount Bassin's conclusions, as the biometric used for fluoride exposure is bone levels at diagnosis—which, being cumulative, can not be used to ascertain fluoride exposure during the critical $6^{th}$ to $8^{th}$ years that is at the heart of Bassin's findings. Another weakness in this study design that may be a further explanation as to why it has not yet been published, is that the controls used in Douglass's study were other bone cancers. Unless Douglass can rule out the possibility that fluoride causes any of these other bone cancers, this was a highly dubious control to choose (Neurath and Connett, 2008).

Furthermore, Douglass revealed an obvious bias towards water fluoridation—and against finding a link between fluoride and osteosarcoma—in a 1991 co-authored paper published as a cover article of the *Journal of the American Dental Association* (McGuire et al., 1991). This article made it very clear how a positive finding on osteosarcoma would end the water fluoridation program, as "Linkage of fluoride ingestion and cancer initiation could result in a large-scale defluoridation of municipal water systems under the Delaney clause," an outcome the authors declared would be "detrimental to the oral health of most Americans, particularly those who cannot afford to pay for increasingly expensive restorative dental care" (McGuire et al., 1991). Such a bias brings into question Douglass's study, the regulatory agencies who selected and funded a less-than-objective oral health researcher to perform a pivotal study on osteosarcoma, and the gullibility of those who wait for such a study to rescue the water fluoridation program.

Also attempting to delay or prevent the determination of carcinogenicity for fluoride is the American Dental Association, one of the most prominent promoters of fluoridation. In March 2009 the California Office of Environmental Health Hazard Assessment solicited public comments on thirty-eight chemicals selected for prioritization for evaluation by the state's Carcinogen Identification Committee (OEHHA, 2009a). "Fluoride and its salts" were included, and in October the state announced that fluoride was one of five chemicals selected for consideration (OEHHA, 2009b). A January 2010 bulletin from the Executive Director of the California Dental Association (CDA), states that the American Dental Association "granted CDA $200,000 to assist in our effort *to prevent the placement* of 'fluoride and its salts' on the List of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity that is produced by the State of California, Environmental Protection Agency; Office of Environmental Health Hazard Assessment (OEHHA)." (our emphasis) (CDA, 2010).

If Bassin's findings are correct, young men with osteosarcoma are dying potentially because they were exposed to fluoridated water in their childhood. Despite the low overall incidence of osteosarcoma, the death of even a single person from this horrible cancer cannot be justified by the slight reduction of dental caries claimed by the proponents of fluoridation. More innocent young men will continue to succumb to this disease the longer it takes for the EPA to make a judgment on this matter. Delaying a decision on the carcinogenicity of fluoride to protect the water fluoridation program is completely unacceptable.

The EPA should **immediately** proceed to a weight of evidence analysis on fluoride and osteosarcoma.

Bassin's is not the only study that raises the possibility that fluoride may cause osteosarcoma (NAS, 1977; NTP, 1990; Hoover et al. 1991; Cohn, 1992; Takahashi, 2001). In the event that Bassin's study cannot be refuted, the weight of evidence should qualify fluoride in the EPA's category of "Likely to Be Carcinogenic to Humans." Here is the EPA's own criteria for establishing that description:

"Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans." Adequate evidence consistent with this descriptor covers a broad spectrum. As stated previously, the use of the term "likely" as a weight of evidence descriptor does not correspond to a quantifiable probability. The examples below are meant to represent the broad range of data combinations that are covered by this descriptor; they are illustrative and provide neither a checklist nor a limitation for the data that might support use of this descriptor. Moreover, additional information, e.g., on mode of action, might change the choice of descriptor for the illustrated examples. Supporting data for this descriptor may include:

- an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments;
- an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans;
- a positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset;
- a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or
- a positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case.

Published studies on fluoride and osteosarcoma satisfy four of these descriptors above. For the first point, see the comments of NRC (2006) above. For the third point, see Bassin et al. (2006). For the fourth point, see the NTP (1990) rat study. For the fifth point, see Hoover et al. (1991); Cohn, (1992); Takahashi et al. (2001); and Bassin et al. (2006).

Thus EPA should identify fluoride as "Likely to Be Carcinogenic to Humans" and set the MCLG for fluoride to zero.

In addition, NRC (2006) recommended that further research be conducted on the effects of fluoride on bladder cancer risk, and suggested that in vivo human genotoxicity studies be carried out within U.S. populations or populations having similar nutritional or sociodemographic variables.

Furthermore, in a bona fide cancer risk assessment the OW must consider the cancer risks of deliberately adding arsenic—a known human carcinogen—above its MCLG of zero, when it sanctions the use of industrial grade silicofluorides as fluoridating agents. The levels of arsenic in the treated water can reach 1 ppb (Hazan, 2000), which has an incremental cancer risk of 1 in 1000 for lifetime consumption.

*2.3. OW has failed to consider fluoride's effects on the brain.*

OW has ignored the voluminous animal and human data that fluoride damages the brain, much of it published since the NRC (2006) review (Appendix A). OW is blindly accepting the claim that fluoridation significantly reduces tooth decay (see Section 2.1.1. above), while cavalierly ignoring the voluminous evidence that fluoride can damage the developing brain. These neurological effects are occurring at levels that offer no adequate margin of safety (as required by the SWDA) to protect the whole population (as we demonstrate below). Does the EPA really believe it is justifiable to risk our children's brains to secure a very small reduction (if any) in tooth decay?

When the NRC (2006) panel looked at the animal and human studies on fluoride's interaction with the brain it concluded:

1) On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means. p. 187.

The NRC panel looked at FIVE IQ studies, and drew special attention to the study by Xiang et al. (2003a), which they considered the best designed.

2) Several studies from China have reported the effects of fluoride in drinking water on cognitive capacities (Li XS, et al., 1995; Zhao et al., 1996; Lu et al., 2000; Xiang et al., 2003a; 2003b). Among the studies, the one by Xiang et al. (2003a) had the strongest design. This study compared the intelligence of 512 children (ages 8-13) living in two villages with different fluoride concentrations in the water. The IQ test was administered in a double-blind manner. The high-fluoride area (Wamiao) had a mean water concentration of 2.47 ± 0.79 mg/L (range 0.57-4.50 milligrams per liter [mg/L]), and the low-fluoride area (Xinhuai) had a mean water concentration of 0.36 ± 0.15 mg/L (range 0.18-0.76 mg/L). The populations studied had comparable iodine and creatinine concentrations, family incomes, family educational levels, and other factors. The populations were not exposed to other significant sources of fluoride, such as smoke from coal fires, industrial pollution, or consumption of brick tea. Thus, the difference in fluoride exposure was attributed to the amount in the drinking water. Mean urinary fluoride[1] concentrations were found to be 3.47 ± 1.95 mg/L in Wamiao and 1.11 ± 0.39 mg/L in Xinhuai. Using the combined Raven's Test for Rural China, the average intelligence quotient (IQ) of the children in Wamiao was found to be significantly lower (92.2 ± 13.00; range, 54-126) than that in Xinhuai (100.41 ± 13.21; range, 60-128). pp. 205-6.

The IQ scores in both males and females declined with increasing fluoride exposure. The number of children in Wamiao with scores in the higher IQ ranges was less than that in Xinhuai. There were corresponding increases in the number of children in the lower IQ range. Modal scores of the IQ distributions in the two villages were approximately the same. A follow-up study to determine whether the lower IQ scores of the children in Wamiao might be related to differences in lead exposure disclosed no significant

difference in blood lead concentrations in the two groups of children (Xiang et al., 2003b). pp. 205-6.

The NRC (2006) panel's overall conclusion based on its review of these FIVE IQ studies was:

3) A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence. (p. 8)

The NRC (2006) report reproduced the two graphs from the Xiang et al. (2003a) study showing the difference in IQ curves for the two villages for both males and females, and are shown here in Figures 5 and 6.

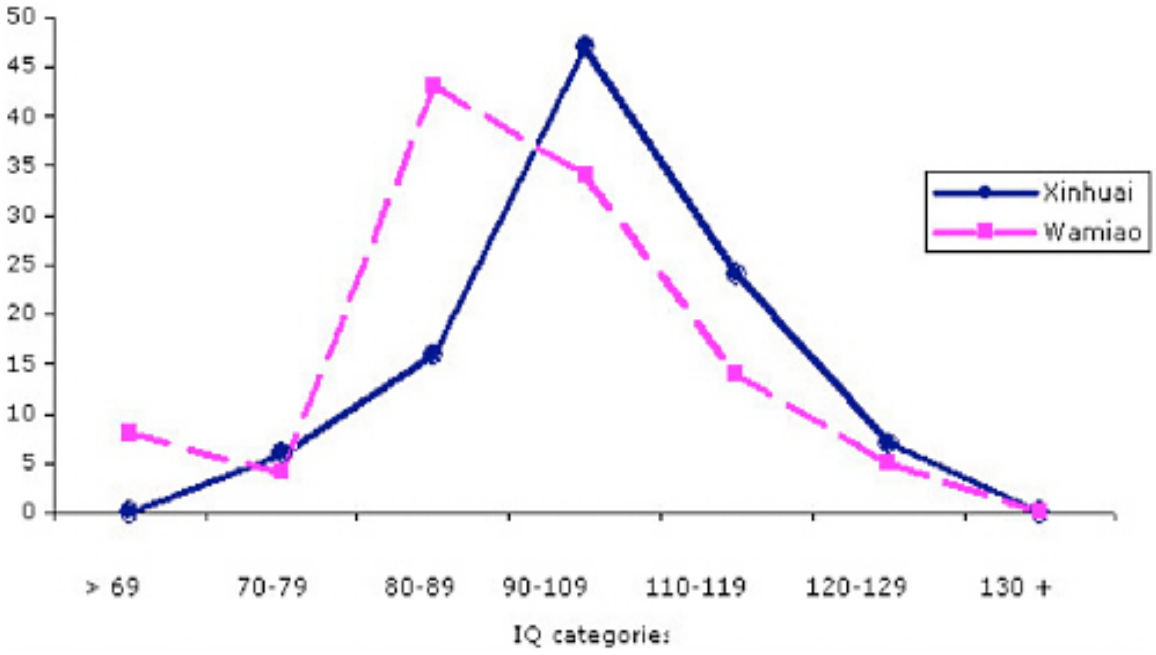


Figure 5. Distribution of IQ scores from males in Wiamiao and Xinuai. Source: data from Xiang et al. 2003a (as shown in NRC, 2006, Figure 7-2, p. 207).

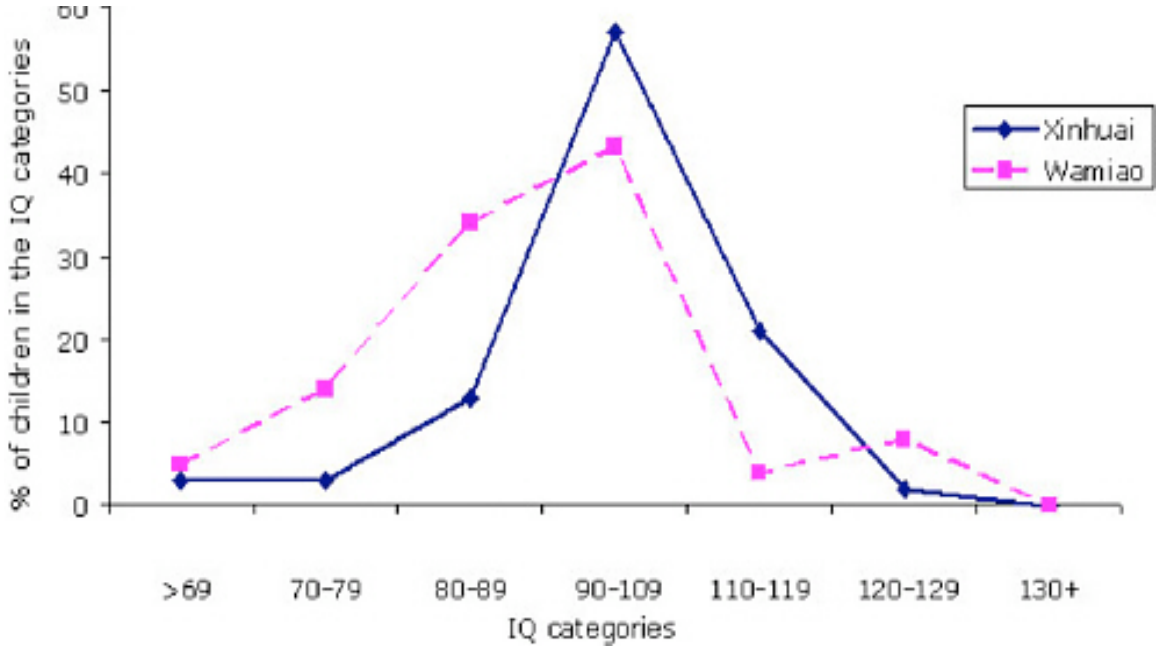


Figure 6. Distribution of IQ scores from females in Wiamiao and Xinuai. Source: data from Xiang et al. 2003a (as shown in NRC, 2006, Figure 7-1, p. 207).

Since the NRC panel wrote its report in 2006 many more animal studies have been published and another FOURTEEN IQ studies (Chen Y, et al., 2008; Ding Y, et al., 2011; Fan ZX, et al., 2007; Guo X, et al., 2008; Hong F, et al., 2008; Liu S, et al., 2008; Qin L, et al., 2008; Ren D, et al., 2008; Rocha-Amador et al., 2007; Seraj et al., 2007; Trivedi et al., 2007; Wang G, et al; 2008; Wang S, et al., 2008; Wang SX, et al., 2007). FAN has kept the EPA informed about these studies, so it cannot be claimed that it is not aware of their existence. A listing of the new studies are included at the end in Appendix A. For 23 of the 24 IQ studies (not including Ding et al., 2011, and Xiang Q, et al., 2010) see Connett P, et al., 2010, Appendix 1.

An updated version of Xiang's (2003a) work, which included new information about the relationship between the level of fluoride in the children's plasma and the IQ lowering, was accepted for publication in *Environmental Health Perspectives* (the journal of the National Institute of Environmental Health Sciences, NIEHS) and made available online on December 17, 2010. This publication was later withdrawn when it was found that some of the other material had been previously published. However, for those who have used criticisms of the methodologies of some of these 24 IQ studies to justify ignoring the issue completely, it is important to note that the Xiang paper successfully passed the peer review process of this important journal.

If the OW had published its health risk assessment soon after NRC review was published in 2006, perhaps they could be excused for accepting only the three end points (severe dental fluorosis, stage II skeletal fluorosis and bone fractures) that the panel recommended at the time as a basis of determining a more protective MCLG. However,

as far as the onerous task of protecting the public from pollutants that might cause harm, the EPA should not have limited itself to the science covered in the NRC report, but instead taken advantage of work that has been published since, especially this important new work on the brain. Science does not stand still. The EPA is obliged to use the best and latest science in fulfilling its mandate to protect the health of the American people. By ignoring the many studies on the brain it is not doing so.

Another IQ study published in 2011 by Ding et al. investigated the effects of low levels of fluoride on IQ. Children were exposed to 0.3 to 3 mg F/L fluoride via drinking water. The authors found a very significant linear correlation ($p < 0.0001$) between fluoride levels in the children's urine and lowered IQ (Figure 7). They calculated that there will be a lowering of IQ by 0.59 points for each increase of 1 mg/L urinary fluoride.

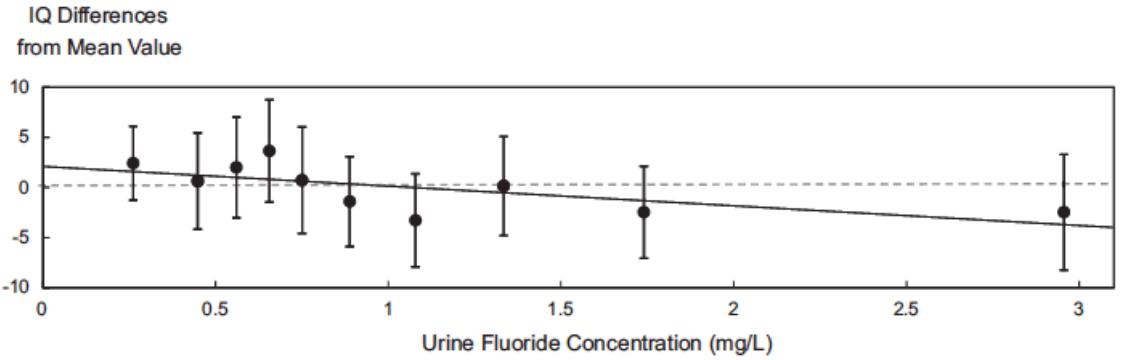


Figure 7. The relationship between IQ differences and urine fluoride concentrations. Multiple linear regression model was carried out to confirm the association of urine fluoride exposure with IQ scores ($F=9.85$, $P<0.0001$). SOURCE: Ding et al., 2011.

Ding et al. (2011) found no obvious level at which fluoride will not have some effect on IQ. Even without applying a safety margin to this finding, it seems there is no safe level that would protect all of America's children from potential interference with mental development from fluoride exposure via the water supply. On this basis, EPA should assign an MCLG of zero for fluoride, as it has done for lead. However, as Ding et al. (2011) states that this is a preliminary finding, and that more work should be done to control for possible confounding factors, the findings of Xiang et al. (2003a; 2003b; 2010) will be employed to determine a safe reference dose for fluoride that will be adequate to protect against lowered IQ in America's children.

Turning to the significance of these brain studies for the determination of a new RfD and MCLG—if OW was to use the data from Xiang et al. (2003a; 2003b) as a starting point in determining an RfD to protect all of America's children, its estimation might go something like this:

Xiang et al. (2003a; 2003b) estimated, via linear extrapolation from all their data, that the lowest water concentration associated with a lowering of IQ (LOAEL) was 1.9 mg F/L. Because these studies only dealt with 500 children—likely with rather homogeneous

genetics, lifestyles and nutritional status—we would need the full uncertainty factor of 10 to account for the full range of sensitivity expected in the whole population of children in the U.S. to arrive at an appropriate RfD for this serious end point. Thus, 1.9 mg F/day divided by 10 = 0.19 mg F/day. The necessity of an uncertainty factor of 10 could also be argued because of the use of a LOAEL, instead of a NOAEL (or we could incorporate both a UF for intraspecies variation and for use of a LOAEL, which would require an uncertainty factor of 100, resulting in an RfD of 0.019 mg/day).

In moving from an RfD to an MCLG, it is EPA policy to consider the 90th percentile water consumer. For infants 0.5 - <1 year, the consumer-only consumption of municipal water at the 90th percentile is 971 mL/day (EPA, 2010b, Table 3-6, p. 69). Thus for this very susceptible age group to remain at or below the RfD of 0.19 mg F/day that would reasonably protect against lowered IQ, the MCLG should be set no higher than 0.2 mg F/L, resulting in a dose of 0.02 mg F/kg/day.

However, if we consider the fluoride contribution from only one other source—fluoridated toothpaste—the situation changes. OW estimates that mean fluoride ingestion from toothpaste for children 0.5 - <1 year is 0.07 mg/day, and that for 1 - <4 year-olds is 0.34 mg/day (EPA, 2010b, Table 6-4, p. 94). Thus, fluoride intake from toothpaste alone contributes nearly half (for 0.5 - <1 year-olds) to twice (for 1 - <4 year-olds) the RfD of 0.19 mg/day that would reasonably protect against lowered IQ. Thus some children will already exceed the safe dose even without the fluoride contribution from water, forcing an MCLG of zero. So whether we consider the preliminary study by Ding et al. (2011) or the studies by Xiang et al. (2003a; 2003b; 2010), it is difficult to understand how the MCLG for fluoride could be set any higher than ZERO.

OW considers 0.05 mg F/kg/day to be the intake necessary to protect teeth from caries (EPA, 2010a, p. xiv). This means that, for the most sensitive child, the level "required" to protect their teeth may more than twice the dose that potentially damages their brain. At this point common sense should take over, and OW should realize that any policy insisting that the health of children's teeth is more important than the health of their brains is misguided and potentially dangerous. EPA's protection of the practice of artificial water fluoridation should end immediately. More effective and less systemically damaging means are currently available to deliver fluoride directly to the teeth, and many other countries have successfully implemented alternative oral health schemes. By bowing to the interests of those promoting fluoridation, EPA's OW has compromised its role as protector of the American people.

*2.4. OW has failed to consider fluoride as an endocrine disruptor.*

The effects of fluoride exposure on the endocrine system are well documented, yet OW has completely ignored these effects in its analysis. According to NRC (2006), fluoride is "an endocrine disruptor in the broad sense of altering normal endocrine function." (p. 266). This altered function can be involve the thyroid, parathyroid, and pineal glands, as well as the adrenals, the pancreas, and the pituitary (NRC, 2006). Fluoride exposure in humans can lead to "elevated TSH with altered concentrations of T3 and T4, increased calcitonin activity, increased PTH activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity." (NRC, 2006, p. 260). Several of these effects are associated with average intakes of 0.05 to 0.10 mg/kg/day (0.03 mg/kg/day with iodine deficiency)—the range wherein the OW's proposed RfD of 0.08 mg/kg/day lies.

According to the American Thyroid Association (ATA, 2003), 2-3% of Americans have pronounced hypothyroidism, and as many as 10-15%—perhaps have subclinical hypothyroidism. Synthroid and Armour, both pharmaceuticals used to treat hypothyroidism (PubMed Health, 2008; 2011) were the 7$^{th}$ and 73$^{rd}$ top selling drugs in the United States in 2009, with over 24 million combined units sold (Drugs.com, Undated). The rate of primary (i.e. at birth) congenital hypothyroidism has increased by 75% over the past two decades in the United States, with the incidence being higher for Hispanic newborns than for white newborns (Olney et al., 2010).

NRC (2006, p. 256) states that "fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans." The pineal gland is a calcifying tissue that can accumulate fluoride, with fluoride concentrations being positively related to calcification (Luke 1997; 2001). Increased calcification of the pineal gland may be associated with a decreased number of functioning pinealocytes and with the ability to produce melatonin (Kunz et al., 1999). Higher intakes of fluoride have been associated with decreased melatonin output in pre-pubescent gerbils, and with earlier sexual maturation in the females (Luke, 1997). Schlesinger et al. (1956) reported that girls living in a fluoridated community reached menarch 5 months earlier than girls living in a non-fluoridated community, and Farkas et al. (1983) reported that postmenarcheal girls were present at younger ages in the town with higher fluoride levels compared to the low-fluoride town. Between 2004 and 2006, the onset of pubertal maturation was 8 years of age for 43% of Blacks, 31% of Hispanics, and 18% of Caucasian girls in the United States—for Caucasian girls, this is double the rate found in 1997 (Biro et al., 2010).

In light of research findings, NRC (2006) offered the following recommendation: "The effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States." (p. 267). It is unfortunate that the OW has ignored the effects that fluoride undoubtedly has on the endocrine system.

*2.5. OW has failed to consider the disproportionate impact on a number of susceptible populations in its analysis.*

In Chapter 2 of the NRC (2006) report, the authors showed that various subsets of the population are likely to exceed the EPA's IRIS reference dose for fluoride of 0.06 mg/kg/day. These include infants <6 months old, people with kidney dysfunction, the elderly, athletes, those working outdoors in hot climates, military personnel, and those with endocrine dysfunctiom (e.g. hypothyroidism). We would add to this list other subsets that are likely to be disproportionally impacted by fluoride. These include pregnant women and fetuses, minorities, low-income families, those with inadequate diets, and those with fluoride sensitivity.

*2.5.1. OW has disregarded pregnant women and embryos/fetuses in its analysis.*

It is well documented that fluoride readily crosses the placenta (Shen and Taves, 1974; Ron et al., 1986; Caldera et al., 1988; Forestier et al., 1990; Gupta et al., 1993; Malhotra et al., 1993; Chlubek et al., 1994; Shimonovitz et al., 1995; Montherrat-Carret et al, 1996; Opydo-Szymaczek and Borysewicz-Lewicka, 2007). Thus the maternal burden of fluoride passes to her unborn child, which can then pass through the blood-brain barrier and damage the developing brain.

In addition to increased fluoride levels in the brain (Du et al., 2008; He et al., 2008; Yu et al., 2008), various neurological alterations have been observed in fetuses of mothers residing in endemic fluorosis areas. These include: reduced numbers of free ribosomes and mitochondria in neurons of the cerebral cortex, nerve cells with swollen mitochondria, reduced rough-surfaced endoplasmic reticulum, expanded granular endoplasm reticulum, grouping of the chromatin, damage to the nuclear envelope and synaptic membrane, reduced number of synapses (He et al., 2008); reduced levels of norepinephrine, 5-hydroxytryptamine, and $\alpha$1-receptor; elevated levels of epinephrine (Yu et al., 2008); reduced mean volume, numerical density, and surface density of neuronal mitochondria (Du et al., 2008).

Neonates of mothers residing in areas with high ($\geq$1.7 mg/L) fluoride levels in the drinking water were found to have impaired neurobehavioral capability and agonistic muscle tension, and thus a significantly lower overall neonatal behavioral neurological assessment (NBNA) score compared to those from low (<1.0 mg/L) fluoride areas (Li J, et al., 2008). At least 24 studies have indicated an association between increasing levels of fluoride and reduced IQ in children (Connett P, et al., 2010).

The developing embryo and fetus are undoubtedly the most susceptible of all life stages to environmental toxins. Damage to the brains and bodies of the developing embryo and fetus can have lifelong implications, and thus special consideration should be given to this group when determining an RfD for fluoride that is appropriate for the entire population.

*2.5.2. OW has completely ignored infants 0-6 months of age in its analysis, and has failed to consider the disproportionate burden placed on bottle-fed infants.*

Due to their small size and rapid development, infants are at an elevated risk for suffering from the toxic and often irreversible effects of fluoride. Yet, OW has refused to consider this extremely vulnerable subpopulation in its calculations. The rationale behind the decision to exclude infants less than 6 months of age is that this is not a critical period for the development of dental fluorosis, as the "mineralization of the secondary teeth begins at about 6 $\pm$ 2 months with the incisors" (Massler and Schour, 1958).

Despite the very real possibility that various other tissues and organs besides the teeth are at risk for developmental abnormalities in response to fluoride exposure prior to 6 months of age, it is grossly negligent of the OW—even when only considering the risk of dental fluorosis—to ignore infants younger than 6 months old. A mean age of 6 months, as calculated by Massler and Schour (1958), means that mineralization of secondary teeth begins for many infants at 4 months of age, and even earlier for others. By setting the lower limit of the critical period for the development of dental fluorosis at 6 months, perhaps 50% of infants would not be protected from developing dental fluorosis of permanent teeth. Even more puzzling, however, is OW's assertion that the proposed RfD of 0.08 mg/kg/day is "protective for the endpoints of severe fluorosis in primary teeth" (EPA, 2010a, p. 107). As mineralization "for the primary teeth begins in utero" (Massler and Schour, 1958), then fetuses and infants 0-6 months should certainly be included in this dose-response analysis.

Additionally, many references more recent than the one cited from 1958 discuss the critical period of developing dental fluorosis to be between birth and 8 or 9 years of age. The EPA (1985) and IOM (1997) both use this period. Evans and Stamm (2007) refer to the "presumed start of enamel mineralization (at birth)". Levy et al. (2010), as part of the longitudinal Iowa Fluoride Study (IFS), states that "substantial fluoride intake from both reconstituted powdered infant formula and other beverages with added water during the ages from 3 to 9 months…has the effect of elevating a child's risk of developing fluorosis." Hong et al (2006b), also part of the IFS, states "the age for possible fluorosis development has been generally considered to be the first 6-8 years of life."

OW references Den Besten (1999), who noted that "Because the severity of fluorosis is related to the duration, timing, and dose of fluoride intake, cumulative exposure during the entire maturation stage, not merely during critical periods of certain types of tooth development, is probably the most important exposure measure to consider when assessing the risk of fluorosis." Hong et al. (2006b) states that "fluorosis is most severe when high-level exposure occurs in both the secretory and maturation stages and fluorosis may develop in teeth exposed to excessive fluoride during periods exclusive of the critical period."

While breast-feeding is encouraged as the best source of nutrition for infants, a substantial proportion of American children receive their nutrition solely from milk- or soy-based infant formulas. In fact, at 6 months of age, less than 15% of infants in the

U.S. are exclusively breast-fed (CDC, 2010). When concentrated formula, which already contains up to 0.3 mg F/L (NRC, 2006) is reconstituted with fluoridated water containing up to 1.2 mg F/L, these babies could potentially receive more than 200 times more fluoride than a breast-fed infant, whose mother's milk contains only 0.007 (average in fluoridated and non-fluoridated communities). If a 3 kg newborn consumes ~0.5 L formula per day, the amount of formula recommended by the American Academy of Pediatrics (2010; 75 ml per 0.45 kg body weight), the water used to make that formula could contain no more than 0.2 mg F/L to ensure that the RfD of 0.08 is not exceeded. Presently, a 3 kg newborn receiving 0.5 L soy-based formula (containing up to 0.3 mg F/L) reconstituted with "optimally" fluoridated water (containing 1.2 mg F/L) could receive up to 0.25 mg F/kg/day. This is 25 times the AI set forth by IOM (1997), nearly 4 times the upper limit set forth by IOM (1997), and more than 3 times the proposed RfD.

Many bottle-fed infants will exceed the proposed RfD. In the event that water fluoridation is not ended immediately, at the very least the EPA should be recommending to the DHHS that they support a very precise and well-funded program to warn parents who bottle-feed their babies not to use fluoridated tap water for this purpose.

*2.5.3. OW has failed to consider the disproportionate impact on above-average water consumers, which account for at least 10% of the population.*

OW has decided that it intends to protect only 90% of the U.S. population—i.e. those whose water consumption is less than the $90^{th}$ percentile (e.g. $\leq$2 liters of water per day for adults) with its determinations of a new RfD and MCLG for fluoride. Approximately 10% of the U.S. population—roughly 31 million Americans—drink more than OW has allowed for in their calculations. Included among these are pregnant or lactating women; people with high activity levels (e.g. athletes, workers with physically demanding duties, military personnel); people living in very hot or dry climates, especially outdoor workers; and people with health conditions that affect water intake or sodium metabolism (e.g. diabetes mellitus, diabetes insipidus); those with renal disorders; those taking certain drugs that increase thirst, and those with short-term conditions requiring rapid rehydration (e.g. gastrointestinal upsets or food poisoning) (EPA, 2000; NRC, 2006). These people are not being protected by OW's proposed RfD.

*2.5.4. OW has failed to consider the disproportionate impact on minority Americans.*

According to EPA (2011b):

> Environmental Justice is the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies. EPA has this goal for all communities and persons across this Nation. It will be achieved when everyone enjoys the same degree of protection from environmental and health hazards and equal access to the

decision-making process to have a healthy environment in which to live, learn, and work.

Yet, the OW has ignored racial, ethnic, and socioeconomic differences when determining the level of fluoride considered "safe" for all Americans to consume in drinking water—on a daily basis and over a lifetime—and is therefore ignoring its own stated goals of achieving Environmental Justice for all.

Several of the major studies cited by the OW, particularly Dean (1942) and publications resulting from the longitudinal Iowa Fluoride Study (e.g. Hong et al., 2006 a,b; Levy et al., 2010), included mostly white participants. This is not representative of the racial and ethnic make-up of the United States in the 21st Century.

African Americans consume significantly more total fluids and plain water, and thus receive more fluoride from drinking water, than white children (Sohn et al., 2001). In addition, African Americans are less likely to breastfeed than most other racial groups (CDC, 2010). As breast milk contains very low levels of fluoride, babies fed formula made with fluoridated water could receive up to 200 times more fluoride than a breast-fed baby. Thus, African American infants have a higher risk of being overexposed to fluoride. In fact, African Americans and Hispanics have been shown to be at an increased risk of developing dental fluorosis, and have a higher risk of suffering from the more severe forms of this condition (Russell, 1962; Butler et al., 1985; Williams and Zwemer, 1990; Beltrán-Aguilar et al., 2005; Martinez-Mier and Soto-Rojas, 2010).

Fluoride's toxicity is exacerbated by inadequate nutrition, including lower intakes of iodine and calcium. Certain racial groups are more likely to be lactose intolerant than others. Included among these are Central and East Asians (80-100% lactose intolerant; de Vrese, 2001), Native Americans (80-100% lactose intolerant; National Institute of Child Health and Human Development, 2006), African Americans (75% lactose intolerant), and Southern Indians (70% lactose intolerant; de Vrese, 2001). The elevated incidence of lactose intolerance may indicate lower rates of milk consumption, and higher consumption rates of water or other beverages, than Whites (21% lactose intolerant; Scrimshaw, 1988). Thus these groups may be more heavily exposed to fluoride in water and other beverages than are Caucasian Americans, and their calcium intakes may be compromised.

The toxicity of fluoride is also exacerbated by kidney dysfunction and diabetes, which are more prevalent among minorities than whites. Hispanics are nearly twice as likely (American Diabetes Association, 2010)—and African Americans nearly four times more likely (US Renal Data System, 2005)—to develop kidney failure than are Caucasians. Both African Americans and Hispanics are nearly twice as likely to suffer from diabetes than whites (American Diabetes Association, 2010).

*2.5.5. OW has failed to consider the disproportionate burden placed on low-income families.*

Poor nutrition frequently occurs among low-income families. As inadequate nutrition increases the toxicity of fluoride (see Section 2.5.6), low-income children and adults are more susceptible to the detrimental effects of fluoride exposure. Yet the OW has ignored this susceptible subpopulation in its determination of a new RfD. This is another example of OW failing to comply with EPA's stated goal of achieving Environmental Justice "for all communities and persons across this Nation" (EPA, 2011a).

As with African Americans, low-income children have been found to consume significantly more total fluids and plain water, and thus receive more fluoride from drinking water, than higher-income children (Sohn et al., 2001). Low-income families also consume substantially less fresh fruits and vegetables—and thus more processed foods—than other groups. Most vegetables have a relatively low (<0.5 ppm) fluoride concentration (EPA, 2010b, p. 21), while processed foods including mechanically deboned chicken, contain higher levels of fluoride.

The inadequate diet often common in low-income families includes reduced calcium and iodine intakes, which are known to increase the toxicity of fluoride (see Section 2.5.6). For example, participants in the Food Stamp Program consumed a significantly smaller percentage of the AI for calcium than did higher-income non-participants (73% versus 83% of AI) (Fox and Cole, 2004).

Also of concern is the inability of low-income families living in fluoridated communities to provide low-fluoride or fluoride-free water to reconstitute infant formula. Low-income families are likely not able to afford expensive filtration systems to remove fluoride from tap water, nor are they likely able to afford bottled water containing low or no fluoride.

Unless OW can verify that all racial, ethnic, socioeconomic, and regional populations were adequately represented in each of the studies and "Market Basket" collections reviewed, OW cannot claim to have identified fluoride exposure patterns representative of all Americans. In addition, while the USDA (2005) database on foods is stated to be the "most comprehensive source of information on the concentrations of fluoride in foods", OW admits that it is "incomplete because many foods found in an average U.S. diet are not included." (EPA, 2010b, p. 20).

*2.5.6. OW has failed to consider the disproportionate harm to people with inadequate nutrition.*

OW is ignoring that fluoride toxicity may be exacerbated by poor nutrition, including deficiencies in iodine, calcium, magnesium, vitamin C (ATSDR, 1993, p.112), selenium, and vitamin D (e.g. ATSDR, 1993, p.112; NRC, 2006). Poor nutrition has been found to increase the incidence and severity of dental fluorosis (Pandit et al., 1940; Murray et al., 1948; Littleton et al., 1999) and skeletal fluorosis (Pandit at al., 1940; Marier et al., 1963;

Fisher et al., 1989; Teotia et al., 1984; Littleton et al., 1999). As mentioned in Section 2.1.2, the dose of fluoride at which disturbed endocrine function occurs is reduced in situations of iodine deficiency (NRC, 2006). Lin et al. (1991), in a UNICEF-sponsored study, found that even modest levels of fluoride in the water (0.88 mg/L vs. 0.34 mg/L) resulted in reduced IQ and increased frequency of hypothyroidism when combined with low iodine, even more so than with iodine deficiency alone. Moreover, the increasing dietary intake of fats in the U.S. may have negative repercussions in terms of fluoride metabolism, as "Diets high in fat have been reported to increase deposition of fluoride in bone and, thus, to enhance toxicity" (HHS, 1991).

### *2.5.7. OW has failed to consider those with impaired kidney function.*

The kidneys are responsible for excreting most of the fluoride from the body (NRC, 2006), which is about 50% of ingested fluoride in a healthy person. Kidneys may be exposed to fluoride concentrations five times greater than other soft tissues (Whitford, 1996), as these organs concentrate fluoride as much as 50-fold from plasma to urine (NRC, 2006). Indeed, with the exception of the pineal gland, the kidneys accumulate more fluoride than any other soft tissue in the body (Hongslo et al., 1980; Ekstrand, 1996; Whitford, 1996). As such, the potential for fluoride-induced damage to the kidneys is likely greater than it is for most other soft tissues (NRC, 2006).

Indications of kidney damage have been associated with even relatively low fluoride exposures. Morphological changes were observed in the kidneys of rats drinking water with 1 mg F/L (McKay et al., 1957; Varner et al, 1998), a concentration that produces plasma fluoride concentrations equivalent to a human consuming $\leq$1.2 mg F/day (Teotia et al., 1978), or 0.017 mg F/kg/day for a 70 kg adult. Plasma fluoride levels in rats as low as 2 umol/L (equivalent to a human intake of perhaps 2.2 mg F/day; Teotia et al., 1978; NRC, 2006, p. 70) significantly decreased the amount of plasma membrane Ca++-pump protein in kidney membranes (Borke and Whitford, 1999). Among children, kidney damage has been revealed in a dose-dependent manner, with effects associated with water containing only 2.6 mg F/L (Liu et al., 2005). Adding to this weight of evidence is that kidney disease is often found to be co-morbid with skeletal fluorosis in humans (Jolly et al., 1980; Reggabi et al., 1984; Lantz et al., 1987; Ando et al., 2001).

For people whose kidney function is already impaired, fluoride toxicity can be exacerbated (ATSDR, 1993). Renal clearance of fluoride is dependent on pH and glomerular filtration rate (NRC, 2006, p.91). Those with impaired renal function are unable to excrete fluoride efficiently, and thus accumulate fluoride more quickly than a healthy individual (Johnson et al., 1979; Bober, 2006; NRC, 2006).

Although often overlooked, the paper by Mayo Clinic scientists Johnson, Jowsey and Taves (*Fluoridation and bone disease in renal patients*) is extremely important (Johnson et al., 1979). They showed that patients with long-term renal failure were getting bone damage when drinking water with relatively low levels of fluoride in their water. They conclude that:

> "The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride. All of the patients showed increased bone density, and two showed calcification of interosseous ligaments which is thought to be diagnostic of skeletal fluorosis. The average concentration of fluoride in bone of 4.4 moles of fluoride per 100 moles of calcium is equivalent to 9,000 ppm of fluoride on an ash weight basis and is in the middle range of the values that have been reported for advanced fluorosis. The excessive osteoid formation seen in these patients is probably accentuated by fluoride.
>
> ... The meaning of these findings for community fluoridation will depend on whether or not further work will clearly show adverse effects in patients with renal failure drinking water with a concentration of 1 ppm of fluoride and whether these effects can be easily avoided. The finding of adverse effects in patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients imbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed the cause."

For both infant and adult patients with end-stage renal disease (ESRD) undergoing long-term dialysis treatments, plasma fluoride levels were found to be elevated (Armstrong et al, 1980; Warady et al., 1989; al-Wakeel et al., 1997), a condition that when persistent could lead to renal osteodystrophy and other bone damage (Gerster et al., 1983; Pettifor et al., 1989). Fluoride can affect the bone in renal failure patients, for example, by interfering with bone mineralization and increasing osteoid content, and may interact with aluminum to exacerbate osteomalacic lesions (Ng et al., 2004).

The National Kidney Foundation recommends that "Individuals with CKD (chronic kidney disease) should be notified of the potential risk of fluoride exposure" (NKF, 2008). The same year, NKF withdrew its official support for community water fluoridation. OW would be wise to re-analyze its proposed RfD in light of the potential harm to those with kidney dysfunction.

### *2.5.8. OW has failed to consider those co-exposed to lead, arsenic, or aluminum.*

The toxic effects of fluoride have been found to be increased when ingested with certain other elements, including lead, arsenic, and aluminum. Lead has been found to exacerbate dental fluorosis in animal studies (Leite et al., 2011). Fluoride is known to increase aluminum uptake into bone (Ahn et al., 1995; Lubkowska, et al. 2006) and the brain (Varner et al., 1998). Varner et al. (1998) suggested that aluminum facilitates fluoride to cross the blood-brain barrier, and Kaur et al. (2009) found that aluminum "appears to enhance the neurotoxic hazards caused by fluoride" in vivo.

*2.5.9. OW has failed to consider those with an increased sensitivity to fluoride.*

OW is ignoring the evidence that a considerable number of people appear to be very sensitive to fluoride. These people are not being protected by the proposed RfD.
For over 60 years numerous people have claimed to be highly sensitive to fluoride, even at the doses obtained by drinking or bathing with fluoridated water. However, the governments practicing fluoridation have studiously ignored their plight, despite suggestions from independent observers that this issue be resolved on a scientific basis.

Waldbott (1956) reported over 50 similar cases of fluoride sensitivity in the 1950s, and summarized his work in 1982 (published 1998). Waldbott identified a number of symptoms that he collectively referred to as "chronic fluoride toxicity syndrome." These symptoms include various skin rashes, gastrointestinal symptoms, urinary problems, bone and joint pain, neurological symptoms (e.g. headaches, depression), and excessive fatigue not relieved by sleep (Spittle, 2008).

The OW's failure to recognize this problem is perhaps another example of environmental injustice. Although the victims are drawn from across ethnic and socioeconomic lines, it is more often only individuals from higher income levels that are able to discern the cause of their ailments, and that can readily afford avoidance measures. The literature contains anecdotal reports of fluoride-sensitive people whose early symptoms were readily reversed when the source of the fluoride was removed (Waldbott, 1998; Spittle, 2008; Connett P, et al., 2010, Ch.13).

## 3. Conclusions

From the above it is very clear that the EPA's Office of Water (OW) is not meeting the letter of the law in the Safe Drinking Water Act to determine an MCLG (with the RfD being a key stepping stone) which protects everyone "from known and anticipated health effects." Nor is OW meeting the objective of achieving Environmental Justice that EPA director Lisa Jackson has put at the top of the EPA's agenda.

Not only has OW neglected to consider very important health effects of fluoride such as its ability to lower IQ, but even for the limited health effect it has considered – severe dental fluorosis – it has applied an uncertainty factor of 1, which means that no extra allowance has been made to protect minority children or children of low-income families. To make matters even worse, OW is indicating that in its development of a new MCLG it proposes to protect only 90% of the population; OW is ignoring the 10% of the population that consumes over two liters of water per day.

These glaring inadequacies have come about because the OW has taken on the impossible task of trying to determine a "safe" RfD while at the same trying to protect the water fluoridation program. Consideration of presumed benefits (which the OW did not even examine for itself) of a pollutant has no place in the scientific determination of a drinking water goal that is meant to be *safe for everyone*. Had the EPA reviewed the literature on fluoridation's alleged benefits, it would have found the evidence very weak indeed.

There is only one course of action that is both legal and socially just in this matter. The OW must put aside any notion of protecting the fluoridation program, and develop an RfD (and thence an MCLG) that uses the best science and applies appropriate margins of safety to protect the whole U.S. population from <u>all</u> "known and anticipated" harmful effects of fluoride using appropriate margins of safety (or uncertainty factors). The OW documents made public on Jan 7, 2011 entirely fail to do that. The OW should not allow the protection of water fluoridation to distort this process. If water fluoridation is not safe then the EPA should tell the public so, and not play politics with the RfD determination to try to hide the facts.

It has become abundantly clear that the relationship between fluoridation and dental fluorosis is very robust. The higher the level of fluoride in the water, the greater the percentage of children who will develop dental fluorosis in some category. However, the relationship between ingesting fluoride dental caries is very weak to non-existent.

It is also very clear—despite EPA claims to the contrary—that fluoride is not a nutrient. It is not needed for *any* biochemical process. However, it is very toxic for many biological processes. In the early days of fluoridation it was known that fluoride could inhibit enzymes. With time it has become clear that it can interfere with many other biological activities and defense mechanisms, as indicated in the following excerpt from a review article by Barbier et al. (2010):

> "(T)his element interacts with cellular systems even at low doses. In recent years, several investigations demonstrated that fluoride can induce oxidative stress and modulate intracellular redox homeostasis, lipid peroxidation and protein carbonyl content, as well as alter gene expression and cause apoptosis. Genes modulated by fluoride include those related to the stress response, metabolic enzymes, the cell cycle, cell–cell communications and signal transduction."

With the knowledge that 41% of American children ages 12-15 now have some level of dental fluorosis (Beltrán-Aguilar et al., 2010), indicating that they have become over-exposed to fluoride, it is foolish to continue this practice a day longer. Nature gave us the strongest clue that the newborn baby only needs a very, very small—if any—amount of fluoride, as the fluoride content of breast milk is maintained at a very low level (0.004 ppm; NRC, 2006). To continue to expose babies and infants at over 200 times the level of fluoride present in mothers' milk is reckless in the extreme. While it may be difficult for long-term promoters of fluoridation to admit this reality, there is no reason—other than politics—for the EPA to countenance such recklessness. It should return to its proper regulatory role of protecting the population against pollutants in the water, instead of continuing to promote spurious benefits about the safety and efficacy of delivering medicine via the pubic water supply.

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Wallace PE. 2010. Letter to James J. Jones, Deputy Assistant Administrator, Office of Chemical Safety and Pollution Prevention, US EPA, Washington DC; Washington DC, from Perry E. Wallace, Counsel for Objectors, Zelle, Hofmann ,Voelbel & Mason LLP, Washington DC. RE: Docket Nos. OPP-2005-0174 and OPP-2003-0373; Third Demand Letter Concerning Objections to Final Rules Establishing Tolerances for Residues of Sulfuryl Fluoride and Fluoride Anion. November15. Online at http://www.fluoridealert.org/sf-ban/sf.epa-hq-opp-2005-0174-0107-1.pdf

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# APPENDIX A

## Selected studies published since the release of the National Research Council report, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, in March 2006.

*Also available at http://www.fluoridealert.org/since-nrc.html*

| Year | Rough Category | Study | Journal |
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| 2011 | Apoptosis | Wang Z, et al. 2011. Sodium fluoride suppress proliferation and induce apoptosis through decreased insulin-like growth factor-I expression and oxidative stress in primary cultured mouse osteoblasts.<br><br>"**All the tested NaF inhibited proliferation and arrested cell cycle at S phase in osteoblasts, and further demonstrated to induce apoptosis in osteoblasts. On the other hand, we found that NaF increased oxidative stress and decreased protein expression of IGF-I.** Our study herein suggested that NaF caused proliferation suppression, and apoptosis may contribute to decrease IGF-I expression and increased oxidative stress damage by NaF in the primary mouse osteoblasts." | Arch Toxicol. 2011 Apr 2. [Epub ahead of print] Abstract |
| 2011 | Apoptosis | Rocha RA, et al. 2011. Arsenic and fluoride induce **neural progenitor cell** apoptosis. | Toxicol Lett. Mar 22. [Epub ahead of print] Abstract |
| 2011 | Apoptosis | Sun Z, et al. 2011. Fluoride-induced apoptosis and gene expression profiling in **mice sperm in vivo**. | Arch Toxicol. 2011 Feb 22. [Epub ahead of print] Abstract |
| 2011 | Apoptosis | Andrade-Vieira LF, et al. 2011. Spent Pot Liner (SPL) induced **DNA damage** and nuclear alterations in root tip cells of Allium cepa as a consequence of programmed cell death. | Ecotoxicol Environ Saf. 2011 Jan 11. [Epub ahead of print] Abstract |
| 2011 | Apoptosis | Yan X, et al. 2011. Fluoride induces apoptosis and alters collagen I expression in **rat osteoblasts.** | Toxicol Lett. 200(3):133-8. Feb 5. Abstract |
| 2011 | Apoptosis | Xu B, et al. 2011. Effects of the Fas/Fas-L pathway on fluoride-induced apoptosis in **SH-SY5Y cells**. | EnvironToxicol. 26(1):86-92. Feb. Abstract |
| 2011 | Apoptosis | Madusudanan Rao S, et al. 2011. Morphometry of buccal mucosal cells in fluorosis - a new paradigm.<br><br>"Conclusions: **Fluorosis induces oxidative stress, DNA damage and apoptosis** which can | Hum Exp Toxicol. Mar 15. [Epub ahead of print] Abstract |
| 2011 | Apoptosis | Madusudanan Rao S, et al. 2011. Morphometry of buccal mucosal cells in fluorosis - a new paradigm.<br><br>"Conclusions: **Fluorosis induces oxidative stress, DNA damage and apoptosis** which can be the reasons for the increase in the nuclear | Hum Exp Toxicol. Mar 15. [Epub ahead of print] Abstract |

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| 2010 | Apoptosis | Gutiérrez-Salinas J, et al. 2010. Exposure to sodium fluoride produces signs of apoptosis in **rat leukocytes**. | Int J Mol Sci. 11(9):3610-22. Sept. 27. Full Text Article |
| 2010 | Apoptosis | Jacinto-Alemán LF, et al. 2010. In vitro effect of sodium fluoride on antioxidative enzymes and apoptosis during **murine odontogenesis**. | J Oral Pathol Med. 39(9):709-14. Oct. Abstract |
| 2010 | Apoptosis | Gutowska I, et al. 2010. Fluoride as a pro-inflammatory factor and inhibitor of ATP bioavailability in differentiated human THP1 monocytic cells.<br><br>"The incubation of macrophages in fluoride solutions significantly decreased the amount of synthesized cellular ATP and **increased formation of ROS and apoptosis in a dose-dependent pattern**." | Toxicology Letters 196: 74-9. Abstract |
| 2010 | Apoptosis | Lu J, et al. 2010. Proteomics analysis of liver samples from puffer fish Takifugu rubripes exposed to excessive fluoride: an insight into molecular response to fluorosis.<br><br>"… Consistent with their previously known functions, **these identified proteins seem to be involved in apoptosis and other functions associated with fluorosis**. These results will greatly contribute to our understanding of the … **toxicological mechanism of fluoride causing fluorosis in both fish and human**." | J Biochem Mol Toxicol. 24(1):21-8. Jan-Feb. Abstract |
| 2010 | Apoptosis | Salgado-Bustamante M, et al. 2010. Pattern of expression of apoptosis and inflammatory genes in **humans exposed to arsenic and/or fluoride**. | Sci Total Environ. 408(4):760-7. Jan 15. Abstract |
| 2009 | Apoptosis | Karube H, et al. 2009. NaF activates MAPKs and induces apoptosis in **odontoblast-like cells**. | J Dent Res. 88(5):461-5. May. Abstract |
| 2009 | Apoptosis | Yan X, et al. 2009. Effects of sodium fluoride treatment in vitro on cell proliferation, apoptosis and caspase-3 and caspase-9 mRNA expression by **neonatal rat osteoblasts**. | Arch Toxicol. 83(5):451-8. May. Abstract |
| 2009 | Apoptosis | Herai M, et al. 2009. Induction of apoptosis in **human gingival epithelial cells** by sodium fluoride. | Fluoride 42(1):3-8. Jan–March. Full Report |
| 2009 | Apoptosis | Wang H, et al. 2009. Effects of dietary protein and calcium on **thymus** apoptosis induced by | Environ Toxicol. 24(3):218-24. June. |
| 2009 | Apoptosis | Wang H, et al. 2009. Effects of dietary protein and calcium on **thymus** apoptosis induced by fluoride in **female rats (**Wistar rats). | Environ Toxicol. 24(3):218-24. June. Abstract |

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| 2008 | Apoptosis | Lee JH, et al. 2008. Involvement of both mitochondrial- and death receptor-dependent apoptotic pathways regulated by Bcl-2 family in sodium fluoride-induced apoptosis of the **human gingival fibroblasts**. | Toxicology 243(3):340–7. Jan 20. Abstract |
| 2008 | Apoptosis | Tsai CL, et al. Wu PC. 2008. Induction of apoptosis in **rabbit oral mucosa** by 1.23% acidulated phosphate fluoride gel. | Arch Toxicol. 82(2):81-7. Feb. Abstract |
| 2008 | Apoptosis | Chouhan S, et al. 2008. Effects of fluoride on the tissue oxidative stress and apoptosis in **rats**: biochemical assays supported by IR spectroscopy data. | Toxicology 5;254(1- 2):61-7. Dec. Abstract |
| 2007 | Apoptosis | Yan Q, Zhang Y, Li W, Denbesten PK. 2007. Micromolar fluoride alters **ameloblast lineage cells** in vitro. | J Dent Res. 86(4):336-40. April. Abstract |
| 2007 | Apoptosis | Liu K, et al. 2007. Fluoride-mediated apoptosis and disordering of cell cycle distributions during in vitro organ culture of **mouse fetal long bones**. | Fluoride 40(1):19–23. Jan-March. Full Report |
| 2007 | Apoptosis | Guney M, et al. 2007. Effect of fluoride intoxication on **endometrial** apoptosis and lipid peroxidation in rats: role of vitamins E and C. | Toxicology. 231(2- 3):215-23. March 7. Abstract |
| 2007 | Apoptosis | Huang C, et al. 2007. Toxic effects of sodium fluoride on **reproductive function in male mice**. | Fluoride 40(3):162-8. July-Sept. Full Report |
| 2007 | Apoptosis | Matsui H, et al. 2007. Some characteristics of fluoride-induced cell death in **rat thymocytes**: Cytotoxicity of sodium fluoride. | Toxicol in Vitro 21(6):1113-20. Sept. Abstract |
| 2007 | Apoptosis | Zhang M, et al. 2007. Effects of fluoride on the expression of NCAM, oxidative stress, and apoptosis in **primary cultured hippocampal neurons**. | Toxicology 236(3):208-16. July 17. Abstract |
| 2006 | Apoptosis | Yu RA, et al. 2006. Effects of selenium and zinc on **renal** oxidative stress and apoptosis induced by fluoride in rats. | Biomed Environ Sci. 19(6):439-44. Dec. Abstract |
| 2006 | Apoptosis | Xu H, et al. 2006. Effect of sodium fluoride on the expression of bcl-2 family and osteopontin in rat **renal** tubular cells. | Biol Trace Elem Res. 109(1):55-60. Jan. Abstract |
| 2006 | Apoptosis | He LF, Chen JG. 2006. DNA damage, apoptosis and cell cycle changes induced by fluoride in | World J Gastroenterol. 12(7):1144-8. Feb 21. Full |
| 2006 | Apoptosis | He LF, Chen JG. 2006. DNA damage, apoptosis and cell cycle changes induced by fluoride in **rat oral mucosal cells and hepatocytes**. | World J Gastroenterol. 12(7):1144-8. Feb 21. Full Report |

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| 2006 | Apoptosis | Ge Y, et al. 2006. Apoptosis in **brain cells of offspring rats** exposed to high fluoride and low iodine. | Fluoride 39(3);173-8. July-Sept. Full Report |
| 2005 | Apoptosis | Otsuki S, et al. 2005. Possible link between **glycolysis** and apoptosis induced by sodium fluoride. | J Dent Res. 84(10):919-23. Oct. Abstract |
| 2005 | Apoptosis | Sun G, Zhang Y, Sun X. 2005. Experimental study of fluoride toxicity **onosteoblasts during bone formation**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany. | Fluoride 38(3). Sept. See Abstract No. 48. |
| 2005 | Apoptosis | Jiang CX, et al. 2005. [**Relationship between spermatogenic cell apoptosis and serum estradiol level** in rats exposed to fluoride] | Wei Sheng Yan Jiu. 34(1):32-4. January. [Article in Chinese] Abstract |
| 2011 | Asthma | Donoghue AM, et al. 2011. Occupational asthma in the aluminum smelters of Australia and New Zealand: 1991-2006.<br><br>"RESULTS: The incidence of occupational asthma across all smelters combined was highest in 1992 at 9.46/1,000/year, declining to 0.36/1,000/year in 2006; a 96.2% reduction. **The incidence of occupational asthma was correlated with geometric mean total fluoride concentration**, measured as personal samples from employees undertaking anode changing (r(s) □=□0.497, P□<□0.001)." | Am J Ind Med. 54(3):224-31. Mar. Abstract |
| 2010 | Asthma | Abramson MJ, et al. 2010. Is potroom asthma due more to sulphur dioxide than fluoride? An inception cohort study in the Australian aluminium industry.<br><br>"… SO(2) exposure was significantly associated with these symptoms, bronchial hyper-responsiveness (BHR) to methacholine (a feature of asthma), airflow limitation (reduced forced expiratory volume in 1 second/forced vital capacity ratio) and longitudinal decline in lung function. Fluoride exposure was associated with the same outcomes, but less strongly… further modelling suggested that of the known respiratory irritants, SO(2) was more likely than fluoride to be primarily responsible for the symptoms observed. **Fluoride, inhalable dust and SO(2) were the most important airborne contaminants** | Occup Environ Med. Oct;67(10):679-85. Abstract |

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| 2006 | Asthma | Taiwo OA, et al. 2006. Incidence of asthma among **aluminum workers**. | J Occup Environ Med. 48(3):275-82. March. Abstract |
| 2011 | Blood | Amini H, et al. 2011. Drinking Water Fluoride and Blood Pressure? An Environmental Study.<br><br>"… **Statistically significant positive correlations were found between the mean concentrations of F in the GWRs [ground water resources] and the hypertension prevalence of males** (r⍰=⍰0.48, p⍰=⍰0.007), females (r⍰=⍰0.36, p⍰=⍰0.048), and overall (r⍰=⍰0.495, p⍰=⍰0.005). Also, statistically significant positive correlations between the mean concentrations of F in the GWRs and the mean SBP [systolic blood pressure] of males (r⍰=⍰0.431, p⍰=⍰0.018)…" | Biol Trace Elem Res. Apr 12. [Epub ahead of print] Abstract |
| 2010 | Blood | Sawan RMM, et al. 2010. **Fluoride increases lead concentrations** in whole blood and in calcified tissues from lead-exposed rats. | Toxicology 271(1-2): 21-6. April 30. Abstract |
| 2010 | Blood | Gutiérrez-Salinas J, et al. 2010. Exposure to sodium fluoride produces signs of apoptosis in **rat leukocytes**. | Int J Mol Sci. 11(9):3610-22. Sept 27. Abstract |
| 2010 | Blood | Feng P, et al, 2010. Influence of selenium and fluoride on blood antioxidant capacity of rats. "**Fluorosis could induce the decline of blood** | Exp Toxicol Pathol. Dec 10. [Epub ahead of print] Abstract |
| 2010 | Blood | Feng P, et al, 2010. Influence of selenium and fluoride on blood antioxidant capacity of rats. "**Fluorosis could induce the decline of blood antioxidant capacity and the fluidity of erythrocyte membrane, as evident in this study,** and Se at different levels possess some antagonistic effects on blood induced by | Exp Toxicol Pathol. Dec 10. [Epub ahead of print] Abstract |

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| 2009 | Blood | Gutowska I, et al. 2009. Changes in the concentration of fluoride and biogenic elements in the **serum** and bones **of female rats** with stretozotocin-induced diabetes.<br><br>"In our research we observed a **statistically significant increase in the concentration of F in the bones of the diabetic rats, with a simultaneous decrease in the concentration of this element in serum**." | Fluoride 42(1):9-16. Jan-March.<br>Full Report |
| 2007 | Blood | Grucka-Mamczar E, et al. 2007. Influence of extended exposure to sodium fluoride and caffeine on the activity of carbohydrate metabolism enzymes in **rat blood serum and liver**.<br><br>"… Glycolysis in extra-hepatic tissues (serum), under the influence of F, was slightly inhibited; however, it was<br>markedly intensified by caffeine. **Overall, a more profound influence by caffeine on carbohydrate enzyme activity was observed in blood serum (extra-hepatic tissues) than in the liver**." | Fluoride 40(1)62–66. Jan-March.<br>Full Report |
| 2006 | Blood | Opydo-Szymaczek J, et al. 2006. Variations in concentration of fluoride in blood plasma of **pregnant women** and their possible consequences for amelogenesis in a fetus.<br><br>"… Mean value of fluoride concentration in the samples of blood plasma from the 28th week of pregnancy was lower than the mean concentration detected in the 33rd week of pregnancy (**3.29 and 3.73mumol/l, respectively**). These values suggest that apart from drinking water, there were other important sources of fluoride in the examined sample. **The results indicate that a reliable assessment of fluoride exposure in a given population cannot be based solely on the concentration of fluoride in drinking water**…" | Homo. 57(4):295-307.<br>Abstract |
| 2006 | Blood | Shanthakumari D, et al. 2006. Antioxidant defense systems in **red blood cell lysates of men with dental fluorosis** living in Tamil Nadu, India. | Fluoride 39(3):231–9. July-Sept.<br>Full Report |
| 2005 | Blood | Connett M. 2005. Blood fluoride levels as a **tool for assessing risk of fluoride toxicity**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany, | Fluoride 38(3):226.<br>See Abstract Number 9 |
| 2005 | Blood | Connett M. 2005. Blood fluoride levels as a **tool for assessing risk of fluoride toxicity**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany, September. | Fluoride 38(3):226.<br>See Abstract Number 9 |

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| 2005 | Blood | Ruiz-Payan A, et al. 2005. **Chronic effects** of fluoride on growth, **blood chemistry**, and thyroid hormones in adolescents residing in northern Mexico. Paper presented at the XXVIth Conference of the International Society for Fluoride Research (September 26-29). | Fluoride 38(3):246. Full Article (see Abstract Number 37) |
| 2005 | Blood | Xiang Q, et al. 2005. **Serum fluoride and skeletal fluorosis** in two villages in Jiangsu Province, China. | Fluoride 38(3):178–84. Full Report |
| 2011 | Bone | Chen L, et al. 2011. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited.<br><br>" We report five cases of **diffuse periostitis resembling hypertrophic osteoarthropathy** and **perostitis deformans** in lung transplantation patients **on chronic voriconazole, a fluoride-containing compound**…" | Skeletal Radiol. 40(2):143-8. Feb. Abstract |
| 2011 | Bone | Wang Z, et al. 2011. Sodium fluoride suppress proliferation and induce apoptosis through decreased insulin-like growth factor-I expression and oxidative stress in primary cultured mouse osteoblasts.<br><br>"**All the tested NaF inhibited proliferation and arrested cell cycle at S phase in osteoblasts, and further demonstrated to induce apoptosis in osteoblasts. On the other hand, we found that NaF increased oxidative stress and decreased protein expression of IGF-I.** Our study herein suggested that NaF caused proliferation suppression, and apoptosis may contribute to decrease IGF-I expression and increased oxidative stress damage by NaF in the primary mouse osteoblasts." | Arch Toxicol. 2011 Apr 2. [Epub ahead of print] Abstract |
| 2011 | Bone | Yan X, et al. 2011. Fluoride induces apoptosis and alters collagen I expression in **rat osteoblasts.** | Toxicol Lett. 200(3):133-8. Feb 5. Abstract |
| 2010 | Bone | Sawan RMM, et al. 2010. **Fluoride Increases Lead Concentrations in Whole Blood and in Calcified Tissues from Lead-Exposed Rats**. | Toxicology 271(1–2): 21–26. Abstract |
| 2010 | Bone | Itai K, et al. 2010. Serum ionic fluoride concentrations are related to renal function and menopause status but not to age in a Japanese general population. | Clinica Chimica Acta 411: 263–266. Abstract |
| 2010 | Bone | Itai K, et al. 2010. Serum ionic fluoride concentrations are related to renal function and menopause status but not to age in a Japanese general population.<br><br>"Conclusion: SIF [serum ionic fluoride] concentrations in middle-aged healthy | Clinica Chimica Acta 411: 263–266. Abstract |

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| 2010 | Bone | Tu J, et al. 2010. Interactive effect of fluoride burden with calcitonin receptor gene polymorphisms on the risk of **F bone injury**.<br><br>"In this **case-control study, a total of 119 cases and 126 controls were enrolled from 2 aluminum plants in Hubei province**. F burden (UF) was measured by F ion-selective electrode method… RESULTS: The odds of developing F bone injury for participants in the moderate F burden group versus the mild F burden group were 4.1 (95% CI: 1.9, 8.7); the heavy F burden group versus the mild F burden group were 14.1 (95% CI: 6.5, 30.6). The odds of developing F bone injury for participants with the TC & TT genotypes versus the CC genotype were 2.6 (95% CI: 1.4, 4.7). The interactions between TC & TT genotypes and moderate, heavy F burden were significant (OR = 14.4; OR = 40.3). CONCLUSION: The interactive effect of F burden and CTR genotype was significant, which increased the F bone injury risk." | Int Arch Occup Environ Health. Nov 25. [Epub ahead of print]<br>Abstract |
| 2010 | Bone | Song YE, et al. 2010. Effect of fluoride exposure on **bone metabolism indicators ALP, BALP, and BGP**. | Environ Health Prev Med. 2010 Oct 2. [Epub ahead of print]<br>Abstract |
| 2010 | Bone | Shalina TI, Vasil'eva LS. 2010. [**Femoral bone morphogenesis in human fetuses** in the area of environmental fluoride pollution].<br><br>"… In the town of Shelekhov, located closely to the pollution source, the **growth of bones in both length and width, is delayed**. The bone growth was active till week 16, however, **during weeks 18-29, osteoresorption prevailed over the osteosynthesis, the bone thickness decreased, while the activity of their growth in length remained reduced**." | Morfologiia. 137(1):54-7. [Article in Russian]<br>Abstract |
| 2010 | Bone | Xu H, et al. 2010. Activation of PERK signaling through fluoride-mediated endoplasmic reticulum stress in OS732 cells.<br><br>"… **This study proved that PERK signaling play major roles in action of fluoride on osteoblast**, and suggested that bone response in skeletal fluorosis may be due in part to PERK signaling pathway." | Toxicology 277(1-3):1-5. Nov 9.<br>Abstract |
| 2009 | Bone | Levy SM, et al. 2009. **Associations of fluoride intake with children's bone measures at age 11**.<br><br>"… In gender-stratified, and body size- and Tanner stage-adjusted linear regression analyses, associations between girls' bone | Community Dent Oral Epidemiol. 37(5):416-26. Oct.<br>Abstract |

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| 2009 | Bone | Gutowska I, et al. 2009. Changes in the concentration of fluoride and biogenic elements in the serum and **bones of female rats** with stretozotocin-induced diabetes.<br><br>"In our research we observed a **statistically significant increase in the concentration of F in the bones of the diabetic rats, with a simultaneous decrease in the concentration of this element in serum**." | Fluoride 42(1):9-16. Jan-March.<br>Full Report |
| 2008 | Bone | Qu W, et al. 2008. Sodium fluoride modulates **caprine osteoblast proliferation and differentiation**. | J Bone Miner Metab 26(4):328-34. July.<br>Abstract |
| 2007 | Bone | Tamer MN, et al. 2007. **Osteosclerosis** due to endemic fluorosis. | Sci Total Environ. 373(1):43-8. Feb 1.<br>Abstract |
| 2007 | Bone | Tang Q, et al. 2007. Effect of fluoride on expression of pura gene and CaM gene in **newborn rat osteoblasts**. | Fluoride 40(1):31-6. Jan-March.<br>Full Report |
| 2007 | Bone | Chavassieux P, et al. 2007. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease.<br><br>**"fluorosis and osteomalacia"** | Endocrine Reviews 28(2):151–64.<br>Abstract |
| 2007 | Bone | Hallanger Johnson JE, et al. 2007. **Fluoride-related bone disease** associated with habitual tea consumption.<br><br>Figure 1. Lateral lumbar spine showing advanced osteosclerosis of the vertebral bodies, with absence of usual marrow space radiolucency | Mayo Clin Proc. 82(6):719-24. June.<br>• Erratum in: Mayo Clin Proc. 2007 Aug;82(8):1017. dosage error in text.<br>Full Text |
| 2007 | Bone | Kakei M, et al. 2007. Effect of fluoride ions on **apatite crystal formation in rat hard tissues**. | Ann Anat. 189(2):175-81.<br>Abstract |
| 2006 | Bone | Bouletreau PH, et al. 2006. Fluoride exposure and **bone status** in patients with **chronic intestinal failure** who are receiving home parenteral nutrition.<br><br>• TABLE 3. Spinal bone status<br>• TABLE 4. Femoral neck bone mineral density (BMD)<br>• TABLE 5. Frequency of osteopenia and osteoporosis at the beginning and the end of | Am J Clin Nutr. 83(6):1429-37. June.<br>Full Article |
| ~~2006~~ | ~~Bone~~ | ~~Bouletreau PH, et al. 2006. Fluoride exposure~~ and **bone status** in patients with **chronic intestinal failure** who are receiving home parenteral nutrition.<br><br>• TABLE 3. Spinal bone status | ~~Am J Clin Nutr.~~ 83(6):1429-37. June.<br>Full Article |

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| 2006 | Bone | Claassen H, et al. 2006. Extracellular matrix changes in **knee joint cartilage** following bone-active drug treatment. | Cell Tissue Res. 324(2):279-89. May. Abstract |
| 2006 | Bone | Harinarayan CV, et al. 2006. **Fluorotoxic metabolic bone disease:** an osteo-renal syndrome caused by excess fluoride ingestion in the tropics. | Bone 39(4):907-14. Oct. Abstract |
| 2006 | Bone | Clarke E, et al. 2006. **Fluorosis as a probable cause of chronic lameness in free ranging eastern grey kangaroos** (Macropus giganteus).<br><br>"… The significant lesions observed were: osteophytosis of the distal tibia and fibula, tarsal bones, metatarsus IV, and proximal coccygeal vertebrae; osteopenia of the femur, tibia, and metatarsus IV; incisor enamel hypoplasia; stained, uneven, and abnormal teeth wear; abnormal bone matrix mineralization and mottling; increased bone density; and elevated bone fluoride levels. Microradiography of affected kangaroos exhibited "**black osteons**," which are a known manifestation of fluorosis. Collectively, these lesions were consistent with a diagnosis of fluorosis." | J Zoo Wildl Med. Dec;37(4):477-86. Abstract |
| 2005 | Bone | Nyman JS, et al. 2005. Effect of ultrastructural **changes on the toughness of bone**. | Micron 36(7-8):566-82. Abstract |
| 2005 | Bone | Roos J, Dumolard A, Bourget S, Grange L, Rousseau A, 2005. [**Osteofluorosis caused by excess use of toothpaste**.] [Article in French]. | Presse Med. 34(20 Pt 1):1518-20. Nov. Abstract |
| 2011 | Brain: *Animal Studies* | Ge Y, et al. 2011. **Proteomic Analysis of Brain Proteins of Rats Exposed to High Fluoride and Low Iodine**. | Archives of Toxicology Arch Jan;85(1):27-33. Abstract |
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| 2006 | DNA | Zhang Y, et al. 2006. DNA damage induced by fluoride in **rat osteoblasts**. | Fluoride 39(3)191–4. July-Sept. Full Report |
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| 2008 | Dyspepsia | Spittle B. 2008. Dyspepsia associated with fluoridated water. | Fluoride 41(1):89-92. Jan-March. Full Report |
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| 2010 | Exposure | Lockwood G. 2010. Theoretical context-sensitive elimination times for inhalation anaesthetics.<br><br>*Note from FAN: Desflurane, Sevoflurane and Isoflurane all break down to the fluoride ion in the body*.<br><br>"After 4 h of anaesthesia, the model **predicted body content** to be 28 g nitrous oxide, **26 g desflurane, 14 g sevoflurane, or 15 g isoflurane**, and **99.9% brain elimination times were** then 9 h for nitrous oxide, **33 h for desflurane, 52 h for sevoflurane, and 71 h for isoflurane. At this stage of elimination, the whole body still retained between 4% and 13% of the absorbed dose**." | Br J Anaesth. 104(5):648-55. May. Abstract |
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| 2009 | Exposure | Rodrigues MH, et al. 2009. Dietary fluoride intake by children receiving different sources of systemic fluoride. | J Dent Res. 88(2):142-5. Feb. Abstract |
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| 2007 | Exposure | Opydo-Szymaczek J, et al. 2007. Transplacental passage of fluoride in pregnant Polish women assessed on the basis of fluoride concentrations in maternal and cord blood plasma. | Fluoride 40(1):46-50.<br>Full Report |
| 2007 | Exposure | Kanbak M, et al. 2007. Renal safety and extrahepatic defluorination of **sevoflurane** in hepatic transplantations. | Transplant Proc. 39(5):1544-8. June. |
| 2006 | Exposure | Hong L, et al. 2006. **Fluoride intake levels in relation to fluorosis development** in permanent maxillary central incisors and first molars.<br><br>"... As part of the longitudinal Iowa Fluoride Study, subjects were followed from birth to 36 months... Cumulatively from birth to 36 months, average daily intake of 0.04 mg F/kg BW or less carried relatively low risk for fluorosis (12.9% for maxillary central incisors, 6.8% for first molars). Average daily intake of 0.04-0.06 mg F/kg BW showed a significantly elevated risk for fluorosis (23.0% for maxillary central incisors, 14.5% for first molars), while fluorosis risk was even higher for average intake above 0.06 mg F/kg BW (38.0% for maxillary central incisors, 32.4% for first | Caries Res. 40(6):494-500.<br>Abstract |
| 2006 | Exposure | Hong L, et al. 2006. **Fluoride intake levels in relation to fluorosis development** in permanent maxillary central incisors and first molars.<br><br>"... As part of the longitudinal Iowa Fluoride Study, subjects were followed from birth to 36 | Caries Res. 40(6):494-500.<br>Abstract |

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| 2006 | Exposure | Krook LP, Justus C. 2006. Fluoride poisoning of **horses** from artificially fluoridated drinking water. | Fluoride 39(1)3-10. Jan-Mar. Full Report |
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| 2005 | Exposure | Erdal S, et al. 2005. A quantitative look at fluorosis, fluoride exposure, and **intake in children** using a health risk assessment approach. | Environ Health Persp113:111-7. Full Report |
| 2006 | Exposure | Pagliari AV, et al. 2006. Analysis of fluoride concentration in **mother's milk substitutes**. | Braz Oral Res. 20(3):269-74. Abstract |
| 2005 | Exposure | Zuanon ACC, Aranha AMF. 2005. **Mouthwash ingestion** by preschool children. | J Clin Pediatr Dent 30(1):15-18. |
| 2010 | Exposure: Tea | Pehrsson PR, et al. 2010. The fluoride content of select brewed and microwave-brewed black teas in the United States.<br><br>"Conclusions**: … on average, the dry tea contributes 3–4 times as much fluoride to the brewed tea as does the water. The fluoride provided by brewed tea may contribute significantly amounts of F, and should be considered when assessing total daily intake."** | Journal of Food Composition and Analysis. Published ahead of print. Dec 27. |
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| 2010 | Exposure: Tea | Cressey P, et al. 2010. Estimated dietary fluoride intake for New Zealanders.<br><br>"Intake of fluoride was driven by consumption of dietary staples (bread, potatoes), beverages (**particularly tea**, soft drinks, and beer), and the fluoride status of drinking water." | J Public Health Dent. 70(4):327-36. Fall. Abstract |
| 2009 | Exposure: Tea | de Lourdes Azpeitia-Valadez M, et al. 2009. [Risk factors for dental fluorosis in children between 6 and 15 years old].<br><br>"Prepared gaseous drink and **tea consumption**, age in relation to the exhibition | Rev Med Inst Mex Seguro Soc. May-47(3):265-70. June. [Article in Spanish] Abstract |

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| 2008 | Exposure: Tea | Whyte MP, et al. 2008. **Skeletal fluorosis from instant tea**.<br><br>"CONCLUSIONS: **SF [skeletal fluorosis] from habitual consumption of large volumes of extra strength instant tea calls for recognition and better understanding of a skeletal safety limit for this modern preparation of the world's most popular beverage**." | J Bone Miner Res. 23(5):759-69. May.<br>Abstract |
| 2008 | Exposure: Tea | Yi J, Cao J. 2008. **Tea and fluorosis**.<br><br>"… Long-term consumption of high fluoride tea could result in chronic fluoride intoxication. This review summarized those data of the fluoride content in various tea commodities, and estimated the risk of fluorosis caused by high fluoride tea commodities. We also introduced fluorosis caused by tea from case reports, epidemiology observations and animal models… **it is urgent that governmental and international agencies adopt safe standards of fluoride content in tea commodities**." | Journal of Fluorine Chemistry 129:76-81. |
| 2007 | Exposure: Tea | Hallanger Johnson JE, et al. 2007. **Fluoride-related bone disease** associated with habitual tea consumption.<br><br>Figure 1. Lateral lumbar spine showing advanced osteosclerosis of the vertebral bodies, with absence of usual marrow space radiolucency | Mayo Clin Proc. 82(6):719-24. June.<br>• Erratum in: Mayo Clin Proc. 2007 Aug;82(8):1017. dosage error in text.<br>Full Text |
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| 2005 | Exposure: Tea | Sun DJ et al. 2005. Dose-response relationship between **dental fluorosis and fluoride in brick tea**. Presented at the 26th International Society for Fluoride Research in Wiesbaden, Germany (September). | Fluoride 38(3):253.<br>Full Article (see Abstract 47) |

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| 2007 | Fluoridation | Cheng KK, et al. 2007. **Adding fluoride to water supplies**.<br><br>"…If fluoride is a medicine, evidence on its effects should be subject to the standards of proof expected of drugs, including evidence from randomized trials... In the case of fluoridation, people should be aware of the limitations of evidence about its potential harms and that **it would be almost impossible to detect small but important risks (especially for chronic conditions) after introducing fluoridation**…" | British Medical Journal 335(7622):699-702. Full Report |
| 2007 | Fluoridation | Limeback H, Thiessen K, Isaacson R, Hirzy W. 2007. The EPA MCLG for fluoride in drinking water: new recommendations.<br><br>"**Our results indicated that in all calculations the new MCLG for fluoride in drinking water should be at most one tenth (0.4 mg/L) of the current MCLG of 4 mg/L, suggesting that the practice of fluoridation should be re-evaluated."** | Society of Toxicology 46th Annual Meeting, Charlotte, North Carolina, March 25-29. |
| 2007 | Free Radicals | Shanthakumari D, et al. 2007. Effect of fluoride intoxication on the levels of **intestinal antioxidants studied in rats**. | Methods Find Exp Clin Pharmacol. 29(2):93-9. Abstract |
| 2005 | Free Radicals | Krechniak J, Inkielewicz I. 2005. Correlations between fluoride concentrations and free radical parameters in **soft tissues of rats**. | Fluoride 38(4)293–6. Nov.<br><br>Full Report |
| 2011 | Genotoxicity | Podder S, et al. 2011. Reduction in fluoride-induced genotoxicity in **mouse bone marrow cells** after substituting high fluoride-containing water with safe drinking water. | J Appl Toxicol. 2011 Mar 5. doi: 10.1002/jat.1644. Abstract |
| 2010 | Genotoxicity | Podder S, et al. 2010. Fluoride-induced genotoxicity in **mouse bone marrow cells**: effect of buthionine sulfoximine and N-acetyl-l-cysteine. | J Appl Toxicol. 2010 Dec 10. doi: 10.1002/jat.1605. [Epub ahead of print] Abstract |
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| **2008** | **Genotoxicity** | **Podder S, et al. 2008. *In vivo* suppression by fluoride of chromosome aberrations induced by mitomycin-C in mouse bone marrow cells.** | **Fluoride 41(1):40–3. Jan-March.** |
| 2005 | Genotoxicity | Velazquez-Guardarrama, et al. 2005. Genotoxic evaluation of sodium fluoride and sodium perborate in **mouse bone marrow cells**. | Bull Environ Contam and Toxicol. 74: 566-72. |
| 2010 | Haem Biosynthesis Pathway | Chouhan S, et al. 2010. Fluoride-induced changes in haem biosynthesis pathway, neurological variables and tissue histopathology of rats.<br><br>"This study intended to determine the effects of various concentrations of fluoride (1, 10, 50 and 100 ppm) in drinking water for a period of 12 weeks on changes in haem biosynthesis pathway, oxidative stress and neurological variables supported by histopathological observations and fluoride in rats… **Interestingly and most significantly, these changes were more pronounced at lower concentrations of fluoride compared with higher fluoride dose**…These changes support our earlier findings regarding the role of decreased ionic mobility of fluoride ion at higher concentrations, leading to less pronounced toxicity." | J Appl Toxicol. 30(1):63-73. Jan.<br>Abstract |
| 2011 | Heart:<br>*Study on children* | Karademir S, et al. 2011. Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic **parameters in children** - Original Investigation.<br><br>"… We found **statistically significant low T4 levels, hypocalcemia and hyponatremia**, increased QT and QTc interval in children with dental fluorosis. **Our results show that fluorosis might increase risk of arrhythmia indirectly**, due to its hypocalcemic, hypernatremic, and hypothyroidism effects… **Further studies concerning cardiovascular effect of fluorosis in both adults and children are needed**." | Anadolu Kardiyol Derg. 11(2):150-5.<br>Full Report |
| 2011 | Heart | Flora SJ, et al. 2011. **Interactive effect of arsenic and fluoride on cardio-respiratory disorders in male rats**: possible role of reactive oxygen species. | Biometals. Jan 18. [Epub ahead of print]<br>Abstract |
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| 2010 | Heart | Yang E, et al. 2010. Fluoride induces **vascular contraction through activation of RhoA/Rho kinase pathway in isolated rat aortas**. | Environ Toxicol Pharmacol. 29(3):290-296. May. |
| 2006 | Heart | Jeon SB, et al. 2006. A role for **Rho kinase in vascular contraction** evoked by sodium fluoride. | Biochem Biophys Res Commun. 343(1):27-33. April 28. Abstract |
| 2005 | Heart | Cicek E, et al. 2005. Effects of chronic ingestion of sodium fluoride on myocardium in a **second generation of rats**. | Hum Exp Toxicol. 24(2):79-87. Feb. Abstract |
| 2011 | Immune System / Human study | Hernández-Castro B, et al. 2010. **Effect of fluoride exposure on different immune parameters in humans**.<br><br>"*Context:* T regulatory (Treg) cells play an important role in the modulation of the immune response, and are implicated in the pathogenesis of autoimmune diseases… *Conclusion*: Our data suggest that F exposure exerts a complex and relevant effect on Treg cells in humans." | Immunopharmacology and Immunotoxicology, 33(1):169-77. March. Abstract |
| 2011 | Insulin | Lupo M, et al. 2011. Effect of fluoridated water on plasma insulin levels and glucose homeostasis in rats with renal deficiency.<br><br>"... It is concluded that the consumption of fluoridated water from water supply did not affect plasma glucose levels even in cases of animals with renal disease. However, **a resistance to insulin action was demonstrated**." | Biol Trace Elem Res. 140(2):198-207. May. Abstract |
| 2009 | Insulin | García-Montalvo EA, et al. 2009. Fluoride exposure **impairs glucose tolerance** via decreased insulin expression and oxidative stress. | Toxicology 263(2-3):75-83. Sept 19. Abstract |
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| 2008 | Insulin | Menoyo I, et al. 2008. Fluoride-**induced resistance to insulin in the rat**. | Fluoride 41(4):260–9. Oct-Dec. Full Article |
| 2005 | Insulin | Menoyo I et al. 2005. Effect of fluoride on the **secretion of insulin in the rat**. | Arzneimittelforschung 55:455-60. Abstract |

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| 2011 | Iodine | Ge Y, et al. 2011. **Proteomic Analysis of Brain Proteins of Rats Exposed to High Fluoride and Low Iodine**. | Archives of Toxicology Arch Jan;85(1):27-33. Abstract |
| 2009 | Iodine | Wang J, et al. 2009. Chapter 67 - DNA Damage in Brain and Thyroid Gland Cells **due to High Fluoride and Low Iodine**. | Comprehensive Handbook of Iodine, Pages 643-649. Edited by: Victor R. Preedy, Gerard N. Burrow and Ronald Watson. ISBN: 978-0-12-374135-6. Elsevier Inc. |
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