Comments

in response to

Evidence on the Carcinogenicity of Fluoride and Its Salts

July 2011

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

September 6, 2011

Submitted at the request of the
International Academy of Oral Medicine and Toxicology (IAOMT)
8297 Champions Gate Blvd., #193
Champions Gate, FL 33896

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

SENES Oak Ridge Inc.
Center for Risk Analysis

These comments are submitted to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) in response to their July 2011 report, "Evidence on the Carcinogenicity of Fluoride and Its Salts" (OEHHA 2011a), and their July 8, 2011, notice "Announcement of Carcinogen Identification Committee Meeting Scheduled for October 12 and 13, 2011, and Availability of Hazard Identification Materials for Fluoride and Its Salts, and Tris(1,3-dichloro-2-propyl) Phosphate" (OEHHA 2011b). The author of these comments is a professional in the field of risk analysis, including exposure assessment, toxicity evaluation, and risk assessment. She has recently served on two subcommittees of the National Research Council's Committee on Toxicology that have dealt with fluoride toxicology, including the NRC's Committee on Fluoride in Drinking Water. These comments are submitted at the request of the International Academy of Oral Medicine and Toxicology (IAOMT), and their preparation was supported in part by the IAOMT. These comments include some material submitted to OEHHA in May 2009 and December 2009, in response to earlier notices. Opinions and conclusions expressed herein are those of the author.

1. Summary. These comments pertain to "Evidence on the Carcinogenicity of Fluoride and Its Salts" (OEHHA 2011a), which was issued by OEHHA in July 2011 "to provide the CIC [Carcinogen Identification Committee of the OEHHA Science Advisory Board] with comprehensive information on fluoride carcinogenicity for use in its deliberations on whether or not the chemical should be listed under Proposition 65" (OEHHA 2011a). OEHHA has concluded that available evidence for carcinogenicity of fluoride and its salts includes some positive findings in epidemiologic studies and some positive findings in animal carcinogenicity studies. OEHAA has provided a very good summary of potentially relevant mechanisms for fluoride carcinogenicity. OEHHA has also pointed out a detail omitted by many reviews of fluoride toxicity or carcinogenicity, namely that animal studies typically require substantially higher exposures to achieve an effect than do human studies—in other words, humans are much more sensitive to fluoride than are many animals.

Section 2 of these comments identifies several areas where OEHHA could make their report even more "comprehensive" and more valuable to the CIC. Section 3 comments on two recently published papers on fluoride and osteosarcoma in humans, including a paper from Harvard that was published after OEHHA's report was completed. Since the primary source of fluoride exposure for more than 20 million Californians is fluoridated water, Section 4 briefly summarizes the evidence on the oral health benefits of community water fluoridation.

Key issues which OEHHA and the CIC should keep in mind are listed below. These issues are discussed in more detail in Sections 2-4:

1. More than 20 million Californians have routine exposure to fluoride simply through fluoridated drinking water, without consideration of other sources of exposure.
2. Most fluoridated drinking water systems use silicofluorides as the fluoridation chemical; use of silicofluorides is associated with increased blood levels of lead. EPA considers lead to be a probable carcinogen, and California's Proposition 65 list of chemicals has included "lead and lead compounds" since 1992.

3. Most human studies of fluoride carcinogenesis have not considered age- and sex-dependence. Given that increased risk of osteosarcoma has been identified for young males, especially for childhood exposures, studies that do not consider age and sex cannot be considered negative.
4. The available animal studies of fluoride and cancer risk did not include the age range corresponding to the childhood years identified as important in humans and therefore cannot be considered negative.
5. OEHHA has provided a good discussion of possible mechanisms by which fluoride could induce cancer. It is important to note that fluoride concentrations high enough to produce observed in vitro effects are possible in humans with even "ordinary" exposures.
6. The 2007 EPA "review" cited by OEHHA is not an adequate review of the carcinogenicity of sodium fluoride and does not constitute a properly conducted classification of fluoride with respect to carcinogenicity.
7. The 2006 NRC review of fluoride is not consistent with a classification of "not carcinogenic." The options provided by the NRC review include "possible" carcinogen or "probable" carcinogen based on the data available to the NRC, and the NRC report also urges greater precaution concerning risk to humans, given the uncertainties in the data.
8. A 2009 review of osteosarcoma risk factors (Eyre et al. 2009) lists fluoride among "a number of risk factors that emerge with some consistency" and consider fluoride exposure to have a "plausible" role in etiology of osteosarcoma.
9. A recent paper by Comber et al. (2011) cannot address age-specific exposure and cannot detect an increase in cancer risk of less than 70%.
10. A recent paper from Harvard (Kim et al. 2011) uses a poor set of controls and an inadequate exposure endpoint, and it does not include an age-specific analysis. The reported similarity of measured bone fluoride concentrations in cases (median age, 17.6) and controls (median age, 41.3) suggests that the cases had fluoride exposures at least twice those of the controls.

2. Comments on "Evidence on the Carcinogenicity of Fluoride and Its Salts" (OEHHA 2011a).

(2.1) Fluoride chemistry and exposures

(2.1.1) p. 1, paragraph 1; p. 3, section 2.2. "The public is exposed to fluoride ion by drinking fluoridated water and by using fluoride-containing dental products and treatments. Exposure may also occur through naturally present fluoride in foods and beverages, and in some cases by inhalation of fluoride compounds in the air."

The report mentions public exposure to fluoride by drinking fluoridated water and through naturally present fluoride in foods and beverages. OEHHA should clarify (in addition to footnote 3 regarding infant formula; p. 3) that while some items (e.g., tea) contain fluoride primarily from natural sources, most fluoride in processed foods and both commercial and home-

prepared beverages comes from fluoridated water. Exposure is not just from drinking the fluoridated water itself. My December 2009 comments to OEHHA provided some additional information on sources of fluoride exposure and on population subgroups that have above-average or high fluoride exposures.

(2.1.2) p. 3, section 2.1, paragraph 3. "Examples of fluoride compounds that release fluoride ion are fluorosilicic acid and sodium monofluorophosphate."

Regarding fluorosilicic acid and its salt, sodium fluorosilicate, OEHHA should clarify that these compounds (the silicofluorides) are the primary source of fluoride for most fluoridated water systems. The National Research Council (NRC 2006, pp. 52-53) and Coplan et al. (2007) have discussed the available information on the chemistry and toxicology of these compounds, especially at low pH (e.g., use of fluoridated water in beverages such as tea, soft drinks, or reconstituted fruit juices), when their dissociation to free fluoride ion is probably not complete. Associations between silicofluoride use and biological effects in humans have been reported, in particular, elevated levels of blood lead in children and inhibition of acetylcholinesterase activity (reviewed by Coplan et al. 2007). A recent study in rats found significantly higher concentrations of lead in both blood and calcified tissues of animals exposed to both silicofluorides and lead (Sawan et al. 2010). EPA considers lead to be a probable human carcinogen and to have no practical threshold with respect to neurotoxicity (EPA 2004)—in other words, there is considered to be no safe level of lead exposure, and the MCLG for lead is zero (EPA 2009). California's Proposition 65 list of "Chemicals known to the state to cause cancer or reproductive toxicity" has included "lead and lead compounds" as a carcinogen since 1992 and "lead" with respect to developmental effects since 1987 (OEHHA 2011c). Thus, OEHHA should be aware that silicofluoride use is associated with increased blood levels of a human carcinogen (one that is also associated with neurotoxicity and developmental toxicity), apart from the carcinogenicity of fluoride itself.

(2.1.3) p. 3, last paragraph. "Drinking water fluoridation is practiced in some municipalities in California, but not in others, for the purpose of preventing dental caries."

OEHHA should provide numbers, i.e., population sizes with and without fluoridated water. The Centers for Disease Control and Prevention estimates that 21.5 million people out of 36.8 million on municipal water supplies in California had fluoridated water at the end of 2008 (CDC 2010). The CIC should keep in mind the large number of people who have routine fluoride exposures.

OEHHA and the CIC should also keep in mind that the available evidence, correctly interpreted, does not support a caries-preventive effect of fluoridated drinking water. My comments to OEHHA in 2009 provided some information on this issue. A short summary of the evidence is provided in Section 4 of these comments.

(2.1.4) p. 4, line 2. "Fluoride can also be prescribed as a medication for treatment of osteoporosis."

OEHHA should be aware that fluoride is not approved for treatment of osteoporosis in the U.S. (Raisz et al. 2002). In addition, fluoride tablets, etc., for caries prevention, while available by prescription, are considered unapproved drugs (for example, see DailyMed 2011a,b,c), meaning that they "may not meet modern standards of safety, effectiveness, quality, and labeling" (FDA 2011).

(2.2) Carcinogenicity studies in humans

(2.2.1) p. 4, last paragraph, last sentence. "However, not all these studies specifically examined young males."

OEHHA makes a very important point, that many human studies of osteosarcoma (in particular) have not specifically examined young males. Given that Bassin et al. (2006) have specifically identified increased risk for young males exposed to fluoride (ages 4-12, with a peak for exposures at age 6-8 years), studies that have not looked at young males, and especially that have not looked at age-specific exposure of young males, cannot be assumed to be negative. The lack of "clear associations" (p. 4, last paragraph) may simply be due to inadequate or incomplete analysis of the study population.

In addition, the few studies besides Bassin et al. (2006), e.g., Gelberg et al. (1995), that have looked at individual fluoride exposure (as opposed to group or ecologic measures of exposure) have looked only at total fluoride exposure until time of diagnosis or treatment. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time" between initiation and diagnosis of a cancer) cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure.

(2.2.2) p. 5, paragraph 2, regarding the letter to the editor by Douglass and Joshipura (2006)

OEHHA and the CIC should remember that this was a letter, not a research article, and it contains no actual data. It should be noted that Douglass approved Bassin's dissertation (Bassin 2001), on which her paper was based, and both Douglass and Joshipura were coauthors on an earlier paper by Bassin et al. (2004) describing the exposure analysis used in the study. The dissertation (Bassin 2001) and peer-reviewed paper (Bassin et al. 2006) contain essentially the same results. Douglass and Joshipura (2006) mention, but do not provide, an analysis of the fluoride content of bone specimens from the osteosarcoma patients and a lack of association between bone fluoride concentration and excess risk of osteosarcoma; however, fluoride concentration in bones of diagnosed patients constitutes a measure of cumulative fluoride exposure as discussed above, and would not necessarily be expected to be correlated with the risk of osteosarcoma.

After more than five years, the results promised by Douglass and Joshipura in 2006 have only recently appeared in a peer-reviewed journal (Kim et al. 2011). This paper and its major shortcomings are described in more detail in Section 3 of these comments. Rather than refuting

the findings of Bassin et al. (2006), the paper by Kim et al. (2011) actually supports them, in spite of the limitations of the work as reported.

(2.2.3) p. 1, second paragraph. "The possibility that chance, bias, inappropriate analyses or confounding played a role in these findings [by Cohn and by Bassin et al.] could not be ruled out, however."

As pointed out at the top of p. 5 in the OEHHA report, the studies by Cohn (1992) and Bassin et al. (2006) both found an association of osteosarcoma in young males with fluoride exposure, age-specific exposure for the work of Bassin et al. Rather than discount both studies for reasons of possible "chance, bias, inappropriate analyses or confounding," OEHHA and the CIC should be aware that Bassin et al. have used the most appropriate analysis of any study to date, and that other studies that have not examined young males and that have not considered age-specific exposure are probably more subject to wrong answers for reasons of possible "chance, bias, inappropriate analyses or confounding." This would apply particularly to studies that have included both pediatric and geriatric cancers, have not considered age-specific exposures, or have not used relevant measures of individual exposure. For example, the recent paper by Kim et al. (2011), discussed in Section 3 of these comments, included both pediatric and adult cancers, has not considered age-specific exposures, and has not used a relevant measure of individual exposure. In other words, the best available evidence to date indicates an elevated risk for young males, specifically those with the highest individual fluoride exposures during childhood.

(2.2.4) p. 5, last paragraph, regarding the NRC report

OEHHA and the CIC should be aware that while the NRC (2006) did not consider fluoride to be clearly a carcinogen, the NRC also did not consider fluoride to be "clearly not carcinogenic." That leaves "possible" carcinogen and "probable" carcinogen as the only possibilities. The discussion of EPA guidelines and practice (NRC 2006, pp. 334-335, 342-343) would not have been relevant had the NRC considered "clearly not carcinogenic" to be a likely categorization. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances. The NRC (2006) specifically discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, most of the studies are not sensitive enough to identify small or moderate increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007). In particular, a "negative" study that does not address a key condition involved in a "positive" finding (e.g., the failure to include age-specific, individual exposure or to separate young and old people in the analysis) cannot be considered evidence of no risk.

<u>(2.3) Carcinogenicity studies in animals</u>

(2.3.1) pp. 6-7, regarding the NTP studies

The concerns raised publicly about the NTP studies by EPA staff members should be addressed by OEHHA. In particular, the historic controls from previous studies had not had the special low-fluoride diet used for this study, and therefore more properly constitute a low- to mid-range exposed group rather than a control group. This and other concerns were described in a memo within the Environmental Protection Agency (Marcus 1990) and reported in the press (Hileman 1990). These concerns and the testimony before the U.S. Senate of the union representing EPA scientists (Hirzy 2000) should be taken seriously by OEHHA and the CIC, at the very least as constituting some additional review of the NTP studies.

Regarding the 1992 NTP study in particular (which was not made public until 2005), OEHHA should be aware of the caveats described by the NRC (2006, p. 319). In particular, the study did not have sufficient statistical power to detect a low-level effect. In addition, the study did not show increased osteosarcoma with exposure to ionizing radiation, even though that was an expected outcome.

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with a higher incidence in males than in females (Bassin et al. 2006). Sergi and Zwerschke (2008) indicate that 60-75% of cases are in patients between 15 and 25 years old. In the NTP 2-year study, fluoride exposure was begun when the animals were 6 weeks old (NTP 1990), as is typical for NTP and similar studies (Hattis et al. 2004). Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the 1990 NTP study probably corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely, the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas. Therefore, the 1990 NTP study cannot be interpreted as showing no evidence of causation for pediatric osteosarcoma, although, properly interpreted, it does show evidence for causation of geriatric osteosarcoma.

(2.4) Mechanisms

(2.4.1) p. 7, last paragraph continuing to p. 8. "Comparison of bone accumulation of fluoride in rats and humans leads to the conclusion that rats must be exposed to at least an order of magnitude higher fluoride concentration to achieve the same bone concentrations as humans. This should be kept in mind when considering the relevance of rodent experiments to humans."

OEHHA rightly points out that rats require much higher exposures than humans, by at least an order of magnitude (a factor of 10), to achieve the same effects or similar fluoride concentrations in bone or serum (see NRC 2006; 2009). In other words, humans are considerably more sensitive to fluoride than are most animal species that have been studied.

(2.4.2) pp. 9-12, section on genotoxicity and cell transformation

This section should include the NRC's 2009 review of genotoxicity, regarding *in vitro* genotoxic, cytogenetic, or transformational effects (i.e., positive results) at fluoride concentrations at or above about 5 mg/L (NRC 2009, pp. 91-92). This section should also include the paper by Zhang et al. (2009), which describes a new testing system for potential carcinogens, based on induction of a DNA-damage response gene in a human cell line. Sodium fluoride tests positive in this system, as do a number of other known carcinogens, representing a variety of genotoxic and nongenotoxic carcinogenic mechanisms. Known noncarcinogens—chemicals not associated with carcinogenicity—did not test positive. For fluoride, a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in the other systems.

(2.4.3) p. 10, lines 7-12. "With regard to the relevance of high doses, one should keep in mind that fluoride concentrates in the bone, and that it is the concentration of fluoride to which osteoblasts are exposed that would be relevant to a genotoxic mechanism of carcinogenesis. The high doses should not be used as a rationale for dismissing the positive genotoxicity findings."

OEHHA rightly points out that positive genotoxicity findings cannot be dismissed due to a requirement of high doses or high fluoride concentrations (in the genotoxicity studies). As mentioned above, depending on the experimental system investigated, *in vitro* genotoxic, cytogenetic, or transformational effects have typically been reported at fluoride concentrations at or above about 5 mg/L (recently reviewed by NRC 2009; see also Lasne et al. 1988; Aardema et al. 1989; Kishi and Ishida 1993; Aardema and Tsutsui 1995; Oguro et al. 1995; Mihashi and Tsutsui 1996; Gadhia and Joseph 1997; Wang et al. 2004; Lestari et al. 2005; Wu and Wu 1995; Meng et al. 1995; Meng and Zhang 1997). The system described by Zhang et al. (2009) is considerably more sensitive than the older systems for most chemicals examined; a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in the other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006); for people with substantial fluoride intake, serum fluoride concentrations may also reach or exceed 0.5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine well in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (0.07-0.09 mg/kg/day for an adult; NRC 2006). Thus, kidney and bladder cells are probably exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*, especially when the more sensitive system of Zhang et al. (2009) is considered. Based on the results of Zhang et al. (2009), most tissues of the body are potentially at risk if serum fluoride concentrations reach or exceed 0.5 mg/L. In addition, cells in the vicinity of resorption sites in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006, pp. 140-142) and thus are also at risk for genotoxic effects.

OEHHA should be aware that while osteosarcoma is probably the most studied of cancers in humans, with respect to fluoride exposure, other cancer types are also possible. For example, the

NRC (2006, pp. 330-331) specifically describes some positive findings in humans for bladder and kidney cancer, which would be consistent with the genotoxicity findings. The NRC also recommended further research on a possible effect of fluoride on bladder cancer (NRC 2006, p. 338).

(2.4.4) p. 11, next-to-last paragraph. "A few additional genotoxicity studies of fluoride have been published since the 2006 NRC review."

It is important to note that all of these recent studies have shown positive results. The paper by Zhang et al. (2009) should also be included here.

(2.4.5) p. 13, first paragraph. "In humans, osteosarcomas are most common around the knee joint."

OEHHA also describes the high fluoride concentrations to which osteoblasts (p. 10) and immune cells (in the bone marrow, p. 13) are exposed, and the effect of fluoride to stimulate osteoblasts (p. 12). With respect to the effect of fluoride on bones or bone cells, OEHHA should also be aware of the statistically significant increase in "cortical defects" in the bones of children in the fluoridated town in the Kingston-Newburgh study (Schlesinger et al. 1956). One researcher involved in that study considered these cortical defects "striking" in terms of their similarity (in age, sex, and anatomical distribution) to osteosarcoma (Caffey 1955, as cited by NRC 1977). The National Research Council indicated that this result was considered "spurious," but no basis for this conclusion was provided (NRC 1977). However, OEHHA should consider the findings of Schlesinger et al. (1956) and Caffey (1955) as evidence that fluoride does have effects on the bones of young people in the anatomical areas in which osteosarcomas tend to occur. These findings support the possible mechanisms of osteosarcoma that OEHHA describes.

(2.4.6) additional information regarding possible mechanisms

A recent paper from the National Cancer Institute and Harvard (Mirabello et al. 2011a) reported the possible association of several genetic variants with osteosarcoma, including insulin-like growth factor 1 (IGF1). It is worth noting that the one paper (to my knowledge) that has looked at IGF1 response in connection with fluoride exposure reported a significant increase in IGF1 in fluoride-exposed rabbits (Turner et al. 1997; discussed in NRC 2006, pp. 258, 498-499).

<u>(2.5) Other recent reviews</u>

(2.5.1) p. 13, section 4, second paragraph. "Fluoride was reviewed by the U.S. EPA (2007) and classified in Group D (inadequate evidence of carcinogenicity). In explaining this classification, U.S. EPA cited the statement by the National Academy of Sciences (NRC, 2006) that "the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed."

The EPA 2007 review is a reregistration eligibility decision (RED) for sodium fluoride use as a pesticide (EPA 2007a). In fact, this EPA report does not actually provide a classification or a basis for a classification:

> Based on the available data, sodium fluoride has been classified as a "Group D" (inadequate evidence of carcinogenicity). This conclusion is consistent with the recent report by the National Academy of Sciences which concluded that "the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed." (EPA 2007a, p. 8)
>
> "The human health and ecological risk assessment documents and supporting information listed in Appendix C were used . . . . While the risk assessments and related addenda are not included in this document, they are available from . . . ." (EPA 2007a, p. 5)
>
> Appendix C. Technical Support Documents for Sodium Fluoride [including] Sodium Fluoride Toxicology Chapter for the Reregistration Eligibility Decision (RED) Document. . . . (EPA 2007a, p. 44)

The "toxicology chapter" of the RED document (a separate document), also does not provide a classification or a basis for a classification:

> In 1996, the EPA's Office of Prevention, Pesticides, and Toxic Substances classified sodium aluminofluoride (cryolite) as a "Group D" carcinogen (not classifiable as to carcinogenicity), citing the National Toxicology Program's carcinogenicity study of sodium fluoride (NTP, 1990). More recently, the National Acedemy [sic] of Sciences (NAS, 2006) at the request of the EPA, conducted a review of the toxicologic, epidemiologic, and clinical data on fluoride since the 1993 NAS report. With respect to carcinogenicity, the 2006 NAS report concluded that "on the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanism of action in cell systems. . . the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed." This recent conclusion is consistent with the past conclusion of OPPTS regarding carcinogenic potential of fluoride." (EPA 2007b, pp. 7-8)

Several comments are in order here: (1) By 2007, the EPA should have been using a newer (2005) classification system, as discussed in the NRC report (NRC 2006, pp. 334-335, 342-343). (2) EPA's 2007 toxicology chapter (EPA 2007b) includes only the animal studies of carcinogenicity, not the human studies. (3) The primary EPA RED document (EPA 2007a) does not consider oral exposure as relevant, since the pesticide use of sodium fluoride should not involve oral exposure:

> "Dietary exposure to NaF is not expected. Therefore, acute and chronic dietary endpoints were not selected." (EPA 2007a, p. 7)
>
> "Incidental oral exposure to NaF is not expected, based on registered use patterns. Therefore, incidental oral endpoints were not selected." (EPA 2007a, p. 7)

> "Based on registered uses, no dietary exposure to NaF is anticipated and no toxicological dietary endpoints were identified. Therefore, no dietary assessment has been conducted." (EPA 2007a, p. 9)
>
> "The antimicrobial uses of sodium fluoride are not expected to pose a hazard to groundwater or surface water. Therefore, a drinking water exposure and risk assessment has not been performed." (EPA 2007a, p. 9)
>
> "EPA has determined that the currently registered uses of sodium fluoride. . . meet the safety standards under the FQPA [Food Quality Protection Act] amendments. . . and that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers factors of the toxicity, use practices, and environmental behavior noted above for the general population, but also takes into account the possibility of increased susceptibility to the toxic effects of sodium fluoride residues in this population subgroup." (EPA 2007a, p. 24)
>
> "The Agency has determined that analysis of the potential need for a special hazard-based safety factor under the FQPA is not needed at this time. The Agency does not anticipate dietary or drinking water or residential exposures based on the registered use patterns and there are no tolerances or tolerance exemptions for the use of sodium fluoride as an active ingredient. Therefore, an FQPA hazard analysis is not necessary at this time. (EPA 2007a, p. 24)

EPA has clearly ignored the fact that sodium fluoride is in many brands of toothpaste and various dental products, both prescription and non-prescription, and that sodium fluoride is used in some smaller water fluoridation systems. EPA's discussion of sodium fluoride also cannot speak to the issue of whether the silicofluorides might have a different effect on humans than sodium fluoride.

In summary, OEHHA should not consider EPA's 2007 reports to be an adequate review of the carcinogenicity of sodium fluoride, and especially not a classification of fluoride as to carcinogenicity. It is merely a citation of a 1996 classification that is by now obsolete in view of additional information, together with a misinterpretation of the NRC review (NRC 2006) as being consistent with EPA's 1996 classification (see below). As described above, EPA's 2007 reports have major shortcomings with respect to their utility for OEHHA's review of the carcinogenicity of fluoride.

(2.5.2) p. 13, next-to-last paragraph. "The NRC (2006) reviewed the health effects of fluoride in drinking water, and concluded: 'On the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro), the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed.'"

The NRC committee unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone" (NRC 2006, p. 336) even though the overall evidence is "tentative and mixed." Referring to the animal studies, the committee also said that

"the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans" (NRC 2006, p. 317). The committee also discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small or moderate increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk.

While the NRC committee did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the committee did not consider either "insufficient information" or "clearly not carcinogenic" to be applicable. The committee report includes a discussion of how EPA establishes drinking water standards for known, probable, or possible carcinogens (NRC 2006, pp. 334-335, 342-343); such a discussion would not have been relevant had the committee not considered fluoride to be carcinogenic. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances. As mentioned by the NRC, fluoride may be a cancer promoter rather than an initiator, although the two mechanisms are not mutually exclusive.

In the interest of protecting the health of California's citizens, OEHHA should exercise "a greater precaution regarding the potential risk to humans" (NRC 2006, p. 317). OEHHA should recognize the lack of sensitivity of many studies to detect small or moderate effects (see also the discussion by Cheng et al. 2007). OEHHA should explore reasons why some studies have given negative results (e.g., age-specific exposure was not examined, the study design was insufficiently sensitive, the animal exposures started after the most susceptible age) and should try to evaluate factors that may affect the genotoxicity or carcinogenicity of fluoride in various systems. OEHHA cannot, from the available data, consider fluoride to be clearly not carcinogenic. Nor can OEHHA say that the database is not sufficient to indicate at least the "potential to initiate or promote cancers."

(2.5.3) Recent review paper on the epidemiology of bone tumors in children and young adults

A 2009 paper from the United Kingdom has reviewed the epidemiology of malignant bone tumors in children and young adults (Eyre et al. 2009). They describe the limitations of the ecological and case-control studies typically used. They also discuss a variety of possible risk factors for various bone cancers, including genetic, reproductive, medical, growth and developmental, social, non-occupational environmental exposure (both perinatal and childhood), and parental occupational risk factors. Eyre et al. describe the case-control study by Bassin et al. (2006) as finding that "for males diagnosed with osteosarcoma under the age of 20, fluoride level in drinking water was associated with significantly increased risk, with boys at the highest fluoride exposure at the age of seven over five times more likely to get osteosarcoma than those at the lowest level at the same age." Of several studies included in a table of statistically significant associations between childhood non-occupational environmental risk factors and bone tumors in children and young adults, the highest reported risk estimate is that of Bassin et al. for fluoride exposure in males. Fluoride is listed among "a number of risk factors that emerge with some consistency" and consider fluoride exposure to have a "plausible" role in etiology.

3. Comments on recent publications.

Two additional papers on osteosarcoma in humans and a possible relationship to fluoride exposure have recently been published. A paper by Comber et al. (2011) is discussed briefly below. The recent Harvard paper mentioned earlier in these comments (Kim et al. 2011) is discussed in some detail below.

(3.1) Comber et al. (2011)

Comber et al. (2011) compare osteosarcoma rates in nonfluoridated Northern Ireland and in partially fluoridated Republic of Ireland, with the latter data divided between fluoridated and nonfluoridated areas. They report no significant differences in either age-specific or age-standardized incidence rates of osteosarcoma between fluoridated and nonfluoridated areas.

Comber et al. also describe several limitations of their study, including uncertainty about fluoridation status of particular areas (the possibility of misclassification), the possibility that the place of residence at the time of diagnosis may not be an accurate proxy for lifetime exposure to fluoridated water, and the lack of an accurate measure of total fluoride exposure. Perhaps the most important limitation pointed out by Comber et al. is the relative rarity of the cancer and the correspondingly wide confidence intervals of the relative risk estimates. They estimate that the risk for a fluoridated population would need to be at least 1.7 times that of the nonfluoridated population (a 70% increase) for a statistically significant effect to be detected. In other words, fluoride could cause a 50-60% increase in risk of osteosarcoma, and this study would not be able to detect it.

With respect to using the place of residence at the time of diagnosis as a proxy for lifetime exposure to fluoridated water, Comber et al. point out that if fluoride exposure at a specific age is critical to osteosarcoma development (citing Bassin et al. 2006), use of the fluoride estimation at the time of diagnosis is less valuable. In other words, their analysis cannot evaluate the importance of age-specific exposure.

With respect to the lack of an accurate measure of total fluoride exposure, the authors mention that at least one-third of fluoride intake is estimated to come from sources other than drinking water, citing tea, fish, and toothpaste as examples. The authors do not discuss the possibility that variability in total fluoride intake within the Irish populations could overwhelm differences between populations in fluoride intakes from drinking water alone.

In summary, the paper by Comber et al. does not demonstrate an absence of a relationship between fluoride exposure and osteosarcoma, simply that any effect of fluoridated water (as opposed to total fluoride intake) is not large enough to detect by the methods employed.

(3.2) Kim et al. (2011)

The paper by Kim et al. (2011) is part of the Harvard osteosarcoma study. The paper describes a comparison of bone fluoride levels in cases of osteosarcoma and a set of controls. The authors report no significant difference in bone fluoride levels between cases and controls and no significant association between bone fluoride levels and osteosarcoma risk.

To give some context it is important to know that an earlier part of the Harvard osteosarcoma study, namely the work of Bassin et al. (2006; based on a 2001 dissertation by Bassin 2001), reported an association between age-specific fluoride exposure and risk of osteosarcoma, with the highest risks for childhood exposure for young males. Bassin's study involved 103 cases under the age of 20 (median age, 13.7) and 215 matched controls (median age, 14.5; matching based on age, gender, and distance from the hospital) from the orthopedics departments of the same hospitals. Cases were diagnosed between November 1989 and November 1992. Bassin estimated fluoride exposure from drinking water and fluoride supplements or rinses for each participant, for each year of life, based on residential histories. Bassin et al. describe the limitations of their study and point out that additional "studies with larger numbers of osteosarcoma patients, with incidence under age 20, that examine age-specific and sex-specific associations are required to confirm or refute the findings of the current study."

The NRC report (NRC 2006, pp. 329-330) was published shortly before the Bassin et al. paper appeared, but included an analysis of Bassin's dissertation (2001), which reported essentially the same findings. The NRC also reported a personal communication from C. Douglass of the Harvard School of Dental Medicine, describing a second study involving 189 cases and 289 controls. This study was said to include residence history, detailed interviews about water consumption, and fluoride assays of bone specimens and toenails of all subjects. The NRC committee was told that the preliminary results indicated no statistically significant association with fluoride intakes and that the results were expected to be reported in the summer of 2006. The NRC report describes some concerns about possible bias (in either direction) in the selection of controls and the expectation that the study could have limited statistical power to detect a small increase in osteosarcoma risk due to fluoride exposure.

When Bassin's work was published (Bassin et al. 2006), the same issue of the journal contained a letter to the editor by Douglass and Joshipura (2006), both of whom were coauthors on an earlier paper describing Bassin's exposure analysis (Bassin et al. 2004). This letter mentioned that preliminary findings from the second set of cases did not appear to replicate the earlier work (Bassin's study) and indicated that their findings, which were "currently being prepared for publication," did not suggest an overall association between fluoride and osteosarcoma. It also indicated that both a fluoride intake history and a bone specimen were being obtained for each participant, and that their preliminary analysis indicated that the fluoride content of the bone was not associated with excess risk of osteosarcoma. However, this letter provided no data and therefore constitutes no more than an opinion.

The paper by Kim et al. (2011) was submitted to the *Journal of Dental Research* in January 2011 and published electronically in late July 2011. No mention is made of why it took 5 years from the time Douglass and Joshipura indicated that their findings were "currently being prepared for publication." Nor is it obvious why the paper was published in a dental journal, when it does not deal directly with anything related to dentistry. Other recent papers that include some of the same coauthors (specifically, C. Douglass and R.N. Hoover) have been published in cancer research journals, (e.g., Savage et al. 2007; Mirabello et al. 2011a,b,c), as was Bassin's work (Bassin et al. 2006).

Kim et al. (2011) describe a study involving 137 cases (37 ages 0-14, 72 ages 15-29, 13 ages 30-44, and 15 ages 45 and older) and 51 controls, with cases diagnosed between 1993 and 2000.

Although there is mention of "orthopedic" controls (patients with benign tumors or non-neoplastic conditions), only "tumor" controls were in fact used. The selection of cases and controls was affected in part by the need to obtain bone specimens. The cases had a median age of 17.6 years, the controls, 41.3 years. Kim et al. report no significant difference in the median fluoride concentration in bone between matched osteosarcoma case and tumor control in 32 pairs where age matching was possible. In an unmatched analysis of all cases and controls, the median bone fluoride concentration was significantly higher in controls than in cases. The authors conclude that their study "did not demonstrate an association between fluoride levels in bone and osteosarcoma."

The use of an individual measure of fluoride exposure (bone fluoride concentration) is important to note. However, as the authors themselves point out, "if risk is related to exposures at a specific time in life, rather than total accumulated dose, this metric would not be optimal" (Kim et al. 2011). Bone fluoride concentration is a measure of cumulative fluoride exposure to the time of diagnosis and surgery. Given a "lag time" of at least 5 years between initiation and diagnosis of most cancer types, the bone fluoride concentration at time of diagnosis can be affected by fluoride exposures that occurred after the cancer was initiated. Most importantly, a bone fluoride concentration at time of diagnosis says nothing about fluoride exposure at specific ages, so it does not address the key finding of Bassin et al. (2006).

The osteosarcoma cases analyzed by Kim et al. (2011) included 28 individuals aged 30 or older. The actual number of patients under 20 years old is not given, but was said to be too few to provide sufficient statistical power. Thus the cases analyzed by Kim et al. are not fully comparable to the cases analyzed by Bassin et al. While osteosarcoma obviously occurs in adults, the majority of cases occur in children and young adults (Sergi and Zwerschke 2008; Mirabello et al. 2011a,b,c; Savage et al. 2007); Kim et al. (2011) themselves indicate that osteosarcoma is more prevalent in individuals less than 20 years old. Kim et al. have not explained their justification for including older individuals, other than to have large enough numbers to do their statistical analyses. The possibility that different mechanisms are involved in pediatric and geriatric osteosarcoma has not been addressed.

As mentioned, the controls were all patients with malignant bone tumors other than osteosarcoma, apparently because bone samples were more readily available for tumor controls than for other controls (Kim et al. 2011). Kim et al. point out that if "fluoride levels were related to bone cancer in general, the current study design would be unable to detect this. There is no published evidence of such an association." There also is no published evidence clearly demonstrating a lack of such an association. The one small finding that has been published (as part of an appendix to a Public Health Service report) was an excess of Ewing's sarcoma in fluoridated counties as opposed to nonfluoridated counties (Hoover 1991). This was explained as an artifact of the analysis. However, given the distinct lack of adequate analyses of fluoride exposure and other types of bone cancer, the use by Kim et al. (2011) of tumor controls alone obviously has to be regarded with caution.

Bassin et al. (2006) limited their analysis to 103 cases diagnosed before the age of 20 (median age 13.7) and used 215 orthopedic controls (median age 14.5). Kim et al. (2011) used a much broader range of ages among cases, together with a relatively small set of controls very different in age from the cases and who were themselves bone cancer patients. While there were

apparently limitations in selecting controls who could provide bone samples, nevertheless, the result is that the analysis by Bassin et al. had a much better set of controls than did the analysis of Kim et al.

Kim et al. (2011) report a higher median fluoride concentration of controls compared with cases, which they attribute to the older ages of the controls than the cases. Comparison of the distributions of bone fluoride concentrations between cases and controls (Figure, part D) indicates that the ranges are not greatly different. Given that the median age of the controls is more than twice the median age of the cases (41.3 vs. 17.6), the obvious conclusion is not a lack of association between fluoride exposure and osteosarcoma, but considerably higher average exposure (by a factor of 2) in cases and controls, in order to reach similar bone fluoride concentrations. Kim's 2007 dissertation, on which the 2011 paper is based, reports estimates of "median cumulative lifetime water fluoride" of 14.4 ppm × year for the cases and 16.5 ppm × year for the controls[1]. These cumulative exposures together with the median ages of the two groups again indicate higher average fluoride exposure among cases than controls, by a factor of 2. Rather than refuting the work of Bassin et al., these findings by Kim et al. support an association between fluoride exposure and osteosarcoma.

In order to obtain the estimates of median cumulative lifetime water fluoride, Kim had to develop the exposure histories for the individual cases and controls. In addition, her dissertation indicates that the exposure histories were available for the orthopedic (noncancer) controls. Douglass and Joshipura (2006) indicated that exposure histories were being obtained. Any meaningful comparison of Kim's findings with those of Bassin et al. (2011) will require use of the individual exposure histories to look at exposures at various ages, as opposed to just the comparison of bone fluoride concentrations.

As an incidental note, the bone fluoride concentrations reported by Kim et al. (2011, Figure) for both osteosarcoma cases and tumor controls, extend into the range reported for skeletal fluorosis (NRC 2006). Also of note is that Kim et al. (2011) found that a history of broken bones was a significant predictor of osteosarcoma risk. An increased risk of bone fracture has been associated with fluoride exposure in a variety of studies (e.g., NRC 2006; Alarcón-Herrera et al. 2001; Danielson et al. 1992).

4. **Available data do not support a role of community water fluoridation in improving dental health.**

OEHHA (p. 3, last paragraph) indicates that drinking water fluoridation is practiced for the purpose of preventing dental caries. Because fluoridated drinking water is probably the single largest source of fluoride exposure for at least 21.5 million Californians (CDC 2010), the question of whether water fluoridation actually produces a benefit requires further attention.

The University of York has carried out perhaps the most thorough review to date of human studies on effects of fluoridation. Their work (McDonagh et al. 2000) is commonly cited as showing the safety and efficacy of water fluoridation, but it actually does neither (Wilson and

[1] Personal communication from Chris Neurath, who has examined the dissertation in the Rare Books Room of the Harvard Medical Library. To date, it has not been possible to obtain a copy of the dissertation.

Sheldon 2006; Cheng et al. 2007). The report mentions a surprising lack of high quality studies demonstrating benefits, and also finds little evidence that water fluoridation reduces socioeconomic disparities:

> Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken. (McDonagh et al. 2000)
>
> Water fluoridation aims to reduce social inequalities in dental health, but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation. (Cheng et al. 2007)
>
> Evidence relating to reducing inequalities in dental health was both scanty and unreliable. (Wilson and Sheldon 2006)

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

Neither McDonagh et al. (2000) nor the ADA (2005) mentions that fluoride exposure appears to delay the eruption of permanent teeth, although this has been known since the 1940s (Short 1944; NRC 2006). A delay in tooth eruption alters the curve of caries rates with respect to age and complicates the analysis of age-specific caries rates (Psoter et al. 2005; Alvarez 1995; Alvarez and Navia 1989). Specifically, "the longer the length of exposure to the oral environment the greater is the risk of the tooth becoming carious" (Finn and Caldwell 1963; citing Finn 1952). Komárek et al. (2005) have calculated that the delay in tooth eruption due to fluoride intake may explain the apparent reduction in caries rates observed when comparisons are made at a given age, as is usually done.

Most studies of benefits of fluoride intake or fluoridation have failed to account for a number of important variables, including individual fluoride intakes (as opposed to fluoride concentrations in the local water supplies), sugar intake, socioeconomic variables, and the general decline in caries rates over the last several decades, independent of water fluoridation status. When World Health Organization data on oral health of children in various countries are compared, similar declines in caries over time are seen in all developed countries, regardless of fluoridation status (Cheng et al. 2007; Neurath 2005). Finn (1952) provides an extensive review of dental caries in "modern primitive peoples," concluding that they "show less dental caries than do most civilized peoples. . . . Evidence indicates, however, that primitive peoples have an increased caries attack rate when brought into contact with modern civilization and a civilized diet."

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

A number of sources (reviewed by NRC 2006), including the CDC (2001), indicate that any beneficial effect of fluoride on teeth is topical (e.g., from toothpaste), not from ingestion. Featherstone (2000) describes mechanisms by which topical fluoride has an anti-caries effect and

states that "[f]luoride incorporated during tooth development [i.e., from ingested fluoride] is insufficient to play a significant role in caries protection." Also:

> The fluoride incorporated developmentally—that is, systemically into the normal tooth mineral—is insufficient to have a measureable effect on acid solubility. (Featherstone 2000)
>
> The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries. (CDC 2001)

Fluoride concentrations in drinking water or saliva are too low to be contributing significantly to a topical anti-caries effect, especially since most drinking water is not "swished" around the teeth before being swallowed. CDC (2001) states that "The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low—approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas. This concentration of fluoride is not likely to affect cariogenic activity."

The single study that has examined caries experience in relation to individual fluoride intakes at various ages during childhood (the Iowa study) has found no association between fluoride intake and caries experience; caries rates (% of children with or without caries) at ages 5 and 9 were similar for all levels of fluoride intake (Warren et al. 2009). The authors state that "the benefits of fluoride are mostly topical" and that their "findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*" (emphasis in the original). Most of the children with caries had "relatively few decayed or filled surfaces" (Warren et al. 2009). The authors' main conclusion:

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

The national data set collected in the U.S. in 1986-1987 (more than 16,000 children, ages 7-17, with a history of a single continuous residence) shows essentially no difference in caries rates in the permanent teeth of children with different water fluoride levels (Table 1; Fig. 1; data obtained from Heller et al. 1997; similar data can be obtained from Iida and Kumar 2009). Analysis in terms of mean DMFS (decayed, missing, or filled tooth surfaces) for the group (Fig. 2), as opposed to caries prevalence, shows an apparent 18% decrease between the low-fluoride (< 0.3 mg/L) and fluoridated (0.7-1.2 mg/L) groups. In absolute terms, this is a decrease of about 1/2 (0.55) of one tooth surface per child. One possible explanation is delayed tooth eruption, which was not considered in the study. Note that the mean DMFS for the highest fluoride group is higher than for either of the two intermediate groups, also indicating that DMFS scores are not solely a function of water fluoride concentration. When the data are examined by the distribution of DMFS scores (Fig. 3), no real difference in caries experience with respect to water fluoride concentration is observed.

The available data, responsibly interpreted, indicate little or no beneficial effect of water fluoridation on oral health. OEHHA and the CIC should not assume or suppose beneficial effects of community water fluoridation in their considerations of carcinogenic and genotoxic effects of fluoride.

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

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

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

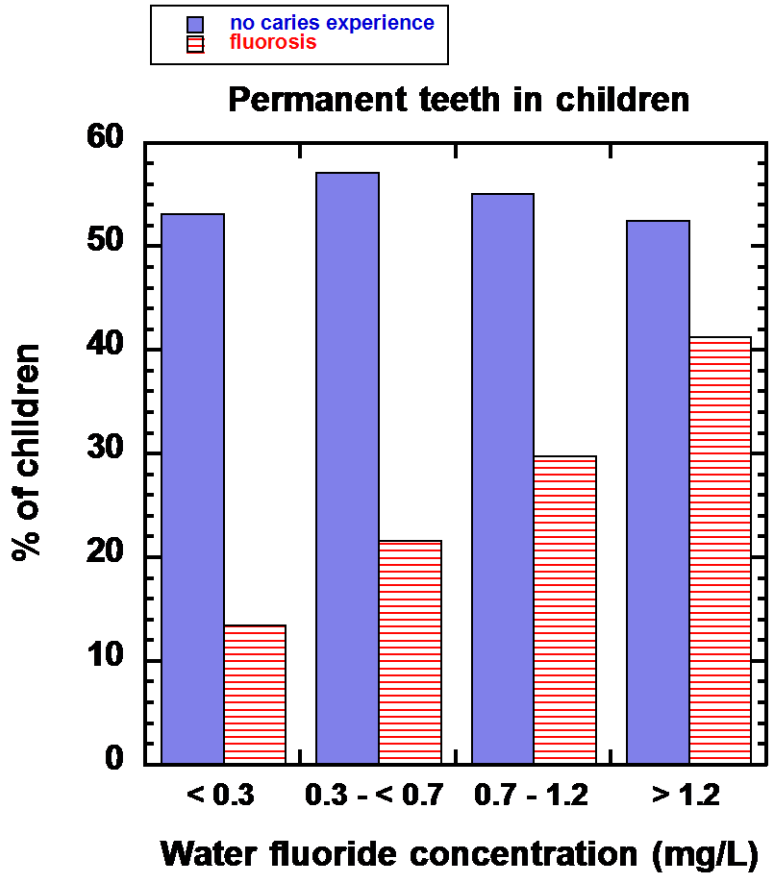

Fig. 1. Percent of children with no caries experience in the permanent teeth (DMFS = 0) and with fluorosis, with respect to water fluoride concentration. Data are shown as % of total children having no caries experience (blue) or having fluorosis (very mild, mild, moderate, or severe, but not questionable; red). Numerical values are provided in Table 1 of these comments and were obtained from Tables 2 and 5 of Heller et al. (1997).

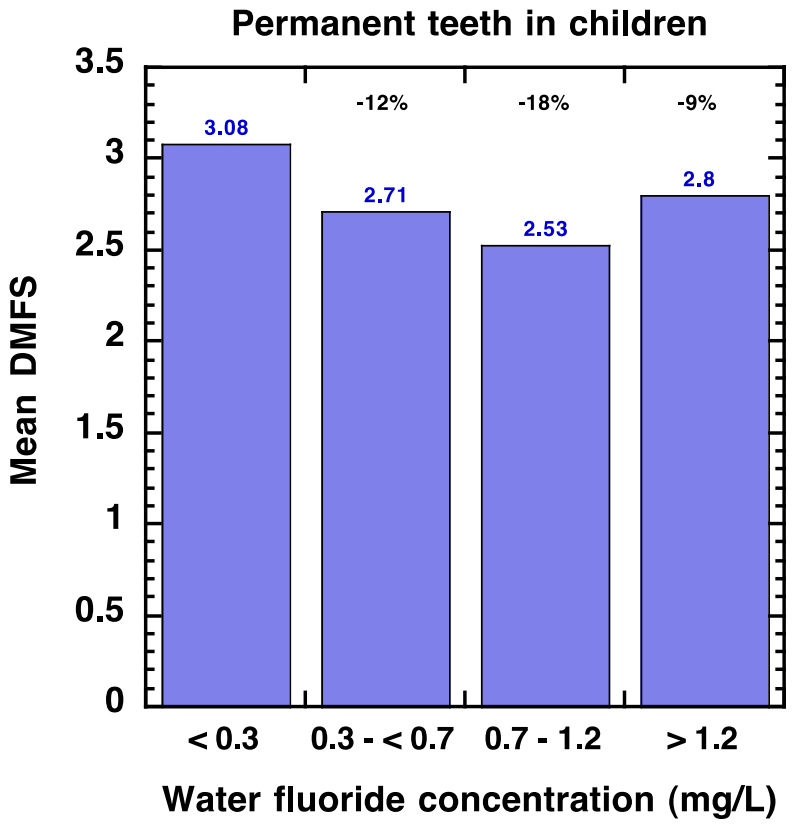

Fig. 2. Mean DMFS score (decayed, missing, or filled permanent tooth surfaces in permanent teeth), with respect to water fluoride concentration. Numerical values are provided in Table 1 of these comments and were obtained from Table 2 of Heller et al. (1997). The percent difference with respect to the lowest fluoride group is also provided.

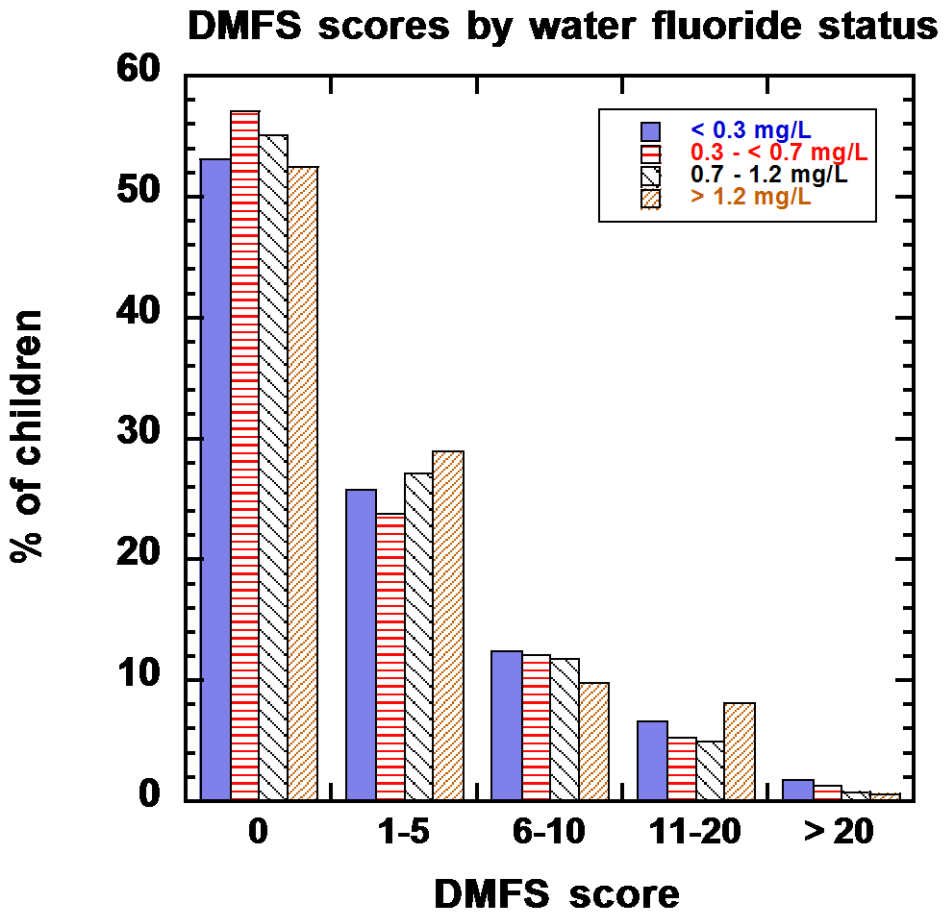

Fig. 3. Percent of children by DMFS score, with respect to water fluoride concentration. Data are shown as % of total children in a given group according to the number of decayed, missing, or filled tooth surfaces in the permanent teeth (DMFS). Data were obtained from Table 2 of Heller et al. (1997).

References

Aardema, M.J., D.P. Gibson, and R.A. LeBoeuf. 1989. Sodium fluoride-induced chromosome aberrations in different stages of the cell cycle: A proposed mechanism. Mutation Research 223:191-203.

Aardema, M.J., and T. Tsutsui. 1995. Sodium fluoride-induced chromosome aberrations in different cell cycle stages. Mutation Research 331:171-172.

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

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

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

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

Bassin, E.B. 2001. Association between fluoride in drinking water during growth and development and the incidence of osteosarcoma for children and adolescents. D.M.S. Thesis, Harvard School of Dental Medicine, Boston, Massachusetts.

Bassin, E.B., M.A. Mittleman, D. Wypij, K. Joshipura, and C.W. Douglass. 2004. Problems in exposure assessment of fluoride in drinking water. Journal of Public Health Dentistry 64(1):45-49.

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

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

Caffey, J. 1955. On fibrous defects in cortical walls of growing tubular bones: their radiologic appearance, structure, prevalence, natural course, and diagnostic significance. Adv. Pediatr. 7:13-51.

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

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

CDC (Centers for Disease Control and Prevention). 2010. 2008 Water Fluoridation Statistics.

Available at http://www.cdc.gov/fluoridation/statistics/2008stats.htm.

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

Cohn, P.D. 1992. A Brief Report on the Association of Drinking Water Fluoridation and the Incidence of Osteosarcoma among Young Males. New Jersey Department of Health, November 8, 1992.

Comber, H., S. Deady, E. Montgomery, and A Gavin. 2011. Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. Cancer Causes Control. Epub ahead of print, April 11, 2011.

Coplan, M.J., S.C. Patch, R.D. Masters, and M.S. Bachman. 2007. Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals. NeuroToxicology 28:1032-1042.

DailyMed (2011a). Fluoride (sodium fluoride) tablet, chewable. Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=58b3e7ff-c032-4e42-823a-8ed7b93d606f (revised May 2011).

DailyMed (2011b). Fluoride drops (sodium fluoride) liquid. Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2e05a9bf-f8e7-41b1-b382-2dc9d8dafee4 (revised May 2011).

DailyMed (2011c). Epiflur TM (sodium fluoride) tablet. Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=97a2ab7a-5a2c-4c35-9bb4-f3cd37dcd180 (revised September 2009).

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

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

EPA (Environmental Protection Agency). 2004. Lead and compounds (inorganic) (CASRN 7439-92-1). Integrated Risk Information System, U.S. Environmental Protection Agency [online]. [Available: http://www.epa.gov/ncea/iris/subst/0277.htm]

EPA (U.S. Environmental Protection Agency). 2007a. Reregistration Eligibility Decision for Sodium Fluoride. EPA 739-R-07-010. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, December 2007.

EPA (U.S. Environmental Protection Agency). 2007b. Memorandum: Sodium Fluoride Toxicology Chapter for the Reregistration Eligibility Decision (RED) Document. PC Code: 075202 (Active). Case No. 3132. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, September 30, 2007.

EPA (Environmental Protection Agency). 2009. 2009 Edition of the Drinking Water Standards and Health Advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water, EPA 822-R-09-011. [Available: http://water.epa.gov/action/advisories/drinking/drinking_index.cfm]

Evans, A.M. 1986. Age at puberty and first litter size in early and late paired rats. Biology of Reproduction 34:322-326.

Eyre, R., R.G. Feltbower, E. Mubwandarikwa, T.O.B. Eden, and R.J.Q. McNally. 2009. Epidemiology of bone tumours in children and young adults. Pediatr. Blood Cancer 53:941-952.

FDA (U.S. Food and Drug Administration). 2011. Unapproved Drugs: Drugs marketed in the United States that do not have required FDA approval. Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm (updated August 5, 2011).

Featherstone, J.D.B. 2000. The science and practice of caries prevention. JADA 131:887-899.

Finn, S.B. 1952. Prevalence of dental caries. In: A Survey of the Literature of Dental Caries. Washington, DC: National Academy of Sciences, Publication 225, pp. 117-173.

Finn, S.B., and R.C. Caldwell. 1963. Dental caries in twins. I. A comparison of the caries experience of monozygotic twins, dizygotic twins and unrelated children. Archives of Oral Biology 8:571-585.

Gadhia, P.K., and S. Joseph. 1997. Sodium fluoride induced chromosome aberrations and sister chromatid exchange in cultured human lymphocytes. Fluoride 30(3):153-156.

Gelberg, K.H., E.F. Fitzgerald, S. Hwang, and R. Dubrow. 1995. Fluoride exposure and childhood osteosarcoma: A case-control study. American Journal of Public Health 85 (12):1678-1683.

Gray, L.E., Jr., V. Wilson, N. Noriega, C. Lambright, J. Furr, T.E. Stoker, S.C. Laws, J. Goldman, R.L. Cooper, and P.M.D. Foster. 2004. Use of the laboratory rat as a model in endocrine disruptor screening and testing. ILAR Journal 45(4):425-437.

Hattis, D., R. Goble, A. Russ, M. Chu, and J. Ericson. 2004. Age-related differences in susceptibility to carcinogenesis: A quantitative analysis of empirical animal bioassay data. Environmental Health Perspectives 112:1152–1158.

Heller, K.E., Eklund, S.A., and Burt, B.A. 1997. Dental caries and dental fluorosis at varying water fluoride concentrations. J. Public Health Dentistry 57(3):136-143.

Hileman, B. 1990. Fluoride bioassay study under scrutiny. Chemical & Engineering News 68(38):29-30 (September 17, 1990).

Hirzy, J.W. 2000. Statement of Dr. J. William Hirzy, National Treasury Employees Union Chapter 280, before the Subcommittee on Wildlife, Fisheries and Drinking Water, United States Senate, June 29, 2000. Available at http://www.nteu280.org/Issues/Fluoride/629FINAL.htm or http://www.fluoridealert.org/HirzyTestimony.pdf.

Hoover, R.N., S.S. Devesa, K.P. Cantor, J.H. Lubin, and J.F. Fraumeni. 1991. Fluoridation of drinking water and subsequent cancer incidence and mortality. Appendix E in: Review of Fluoride Benefits and Risks. Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. U.S. Public Health Service.

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

Kim, F.M., C. Hayes, P.L. Williams, G.M. Whitford, K.J. Joshipura, R.N. Hoover, C.W. Douglass, and the National Osteosarcoma Etiology Group. 2011. An assessment of bone fluoride and osteosarcoma. J. Dent. Res. Epub ahead of print, July 28, 2011.

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

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

Lasne, C., Y.-P. Lu, and I. Chouroulinkov. 1988. Transforming activities of sodium fluoride in cultured Syrian hamster embryo and BALB/3T3 cells. Cell Biology and Toxicology 4(3):311-324.

Lestari, F., A.J. Hayes, A.R. Green, and B. Markovic. 2005. In vitro cytotoxicity of selected chemicals commonly produced during fire combustion using human cell lines. Toxicology in Vitro 19:653-663.

Marcus, W.L. 1990. Fluoride Conference to review the NTP Draft Fluoride Report. Memorandum to A.B. Hais, Acting Director, Criteria & Standards Division, Office of Drinking Water, Environmental Protection Agency.

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

Meng, Z., H. Meng, and X. Cao. 1995. Sister-chromatid exchanges in lymphocytes of workers at a phosphate fertilizer factory. Mutation Research 334:243-246.

Meng, Z., and B. Zhang. 1997. Chromosomal aberrations and micronuclei in lymphocytes of workers at a phosphate fertilizer factory. Mutation Research 393:283-288.

Mihashi, M., and T. Tsutsui. 1996. Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368:7-13.

Mirabello, L., K. Yu, S.I. Berndt, L. Burdett, Z. Wang, S. Chowdhury, K. Teshome, A. Uzoka, A. Hutchinson, T. Grotmol, C. Douglass, R.B. Hayes, R.N. Hoover, S.A. Savage, and for the National Osteosarcoma Etiology Study Group. 2011a. A comprehensive candidate gene approach identifies genetic variation associated with osteosarcoma. BMC Cancer 11:209.

Mirabello, L., R. Pfeiffer, G. Murphy, N.C. Daw, A. Patiño-Garcia, R.J. Troisi, R.N. Hoover, C. Douglass, J. Schüz, A.W. Craft, and S.A. Savage. 2011b. Height at diagnosis and birth-weight as risk factors for osteosarcoma. Cancer Causes Control 22:899-908.

Mirabello, L., E.G. Richards, L.M. Duong, K. Yu, Z. Wang, R. Cawthon, S.I. Berndt, L. Burdett, S. Chowdhury, K. Teshome, C. Douglass, S.A. Savage, and the National Osteosarcoma Etiology Study Group. 2011c. Telomere length and variation in telomere biology genes in individuals with osteosarcoma. Int. J. Mol. Epidemiol. Genet. 2(1):19-29.

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

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

National Academy Press.

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

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

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of sodium fluoride (CAS No. 7681-49-4) in F344/N rats and B6C3F$_1$ mice (drinking water studies). National Toxicology Program Technical Report Series No. 393.

OEHHA (Office of Environmental Health Hazard Assessment). 2011a. Evidence on the Carcinogenicity of Fluoride and Its Salts. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, July 2011.

OEHHA (Office of Environmental Health Hazard Assessment). 2011b. Announcement of Carcinogen Identification Committee Meeting Scheduled for October 12 and 13, 2011, and Availability of Hazard Identification Materials for Fluoride and Its Salts, and Tris(1,3-dichloro-2-propyl) Phosphate. July 8, 2011. Available at http://oehha.ca.gov/prop65/hazard_ident/070811hid.html.

OEHHA (Office of Environmental Health Hazard Assessment). 2011c. Chemicals Known to the State to Cause Cancer or Reproductive Toxicity. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, September 2, 2011. Available at: http://www.oehha.ca.gov/prop65/prop65_list/Newlist.html.

Oguro, A., J. Cervenka, and K. Horii. 1995. Effect of sodium fluoride on chromosomal ploidy and breakage in cultured human diploid cells (IMR-90): An evaluation of continuous and short-time treatment. Pharmacology and Toxicology 76:292-296.

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

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

Raisz, L.G., B.E. Kream, and J.A. Lorenzo. 2002. Metabolic bone disease. In: Williams Textbook of Endocrinology, 10th Ed., P.R. Larsen, H.M. Kronenberg, S. Melmed, and K.S. Polonsky, eds. Philadelphia, PA: Saunders, pp. 1373-1410.

Savage, S.A., L. Burdett, R. Troisi, C. Douglass, R.N. Hoover, and S.J. Chanock. 2007. Germ-line genetic variation of TP53 in osteosarcoma. 2007. Pediatr. Blood Cancer 49:28-33.

Sawan, R.M.M., Leite, G.A.S., Saraiva, M.C.P., Barbosa, F. Jr., Tanus-Santos, J.E., and Gerlach, R.F. 2010. Fluoride increases lead concentrations in whole blood and in calcified tissues from lead-exposed rats. Toxicology 271(1-2):21-26.

Schlesinger, E.R., D.E. Overton, H.C. Chase, and K.T. Cantwell. 1956. Newburgh-Kingston caries-fluorine study. XIII. Pediatric findings after ten years. J. Am. Dent. Assoc. 52(3):296-306.

Sergi, C., and W. Zwerschke. 2008. Osteogenic sarcoma (osteosarcoma) in the elderly: Tumor delineation and predisposing conditions. Experimental Gerontology 43:1039-1043.

Shiboski, C.H., S.A. Gansky, F. Ramos-Gomez, L. Ngo, R. Isman, and H.F. Pollick. 2003. The association of early childhood caries and race/ethnicity among California preschool children. J. Public Health Dentistry 63(1):38-46.

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

Turner, C.H., Garetto, L.P., Dunipace, A.J., Zhang, W., Wilson, M.E., Grynpas, M.D., Chachra, D., McClintock, R., Peacock, M., and Stookey, G.K. 1997. Fluoride treatment increased serum IGF-1, bone turnover, and bone mass, but not bone strength, in rabbits. Calcif. Tissue Int. 61:77-83.

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

Wang, A.-G., T. Xia, Q.-L. Chu, M. Zhang, F. Liu, X.-M. Chen, and K.-D. Yang. 2004. Effects of fluoride on lipid peroxidation, DNA damage and apoptosis in human embryo hepatocytes. Biomedical and Environmental Sciences 17:217-222.

Warren, J.J., S.M. Levy, B. Broffitt, J.E Cavanaugh, M.J. Kanellis, and K. Weber-Gasparoni. 2009. Considerations on optimal fluoride intake using dental fluorosis and dental caries outcomes—a longitudinal study. Journal of Public Health Dentistry 69(2):111-115.

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

Wu, D.Q., and Y. Wu. 1995. Micronucleus and sister chromatid exchange frequency in endemic fluorosis. Fluoride 28(3):125-127.

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