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Subject: Comment on Hazard Identification Materials - Proposed Chemicals. March 2009
Attachments: OEHHA comments.pdf

Dear Ms. Oshita,

I am submitting the attached set of comments to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment in response to the March 5, 2009, request for comments. A copy of this document is also being submitted by fax. Please let me know if you have difficulty receiving either document or have any questions concerning the comments.

Sincerely,

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Comments on

Prioritization of Chemicals for Carcinogen Identification Committee Review
Proposed Chemicals for Committee Consideration and Consultation
March 2009

Proposition 65 Implementation
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

May 5, 2009

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These comments are submitted to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) in response to their March 5, 2009, notice "Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee" (OEHHA 2009a). 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, including the NRC's Committee on Fluoride in Drinking Water. These comments are being submitted at the request of the International Academy of Oral Medicine and Toxicology (IAOMT), and preparation of these comments has been supported in part by the IAOMT. Opinions and conclusions expressed herein are those of the author.

1. Introduction. These comments pertain to "Fluoride and its salts," as listed in Table 1 of OEHHA's March 2009 document "Prioritization of Chemicals for Carcinogen Identification Review: Proposed Chemicals for Committee Consideration and Consultation" (OEHHA 2009b). Fluoride ion (F^-) and certain fluoride chemicals, in particular the silicofluorides (especially H_2SiF_6 and Na_2SiF_6) that are commonly used to provide fluoride ion in municipal drinking water, should be advanced to the next stage of OEHHA's listing process, including development of hazard identification materials and consideration for listing at a future meeting of the Carcinogen Identification Committee. The comments below address material in the document "Fluoride and Its Salts" previously prepared by OEHHA (OEHHA 2009c) and provide additional information that should be considered by OEHHA.

2. Exposure to fluoride. As noted in the first paragraph of the OEHHA document "Fluoride and Its Salts" (OEHHA 2009c), fluoride exposures come from a variety of sources, including drinking water, toothpaste and other dental products, some soils and plants, and occupational exposures. Other sources of human exposures to fluorides that should be considered include pesticides, pharmaceuticals, and industrial air pollution. The National Research Council's 2006 report on Fluoride in Drinking Water includes an extensive survey and summary of fluoride exposures in the U.S. from all sources (NRC 2006a, Chapter 2 and Appendix B).

For most of the U.S. population, including a considerable fraction of the California population, the single largest source of fluoride exposure is municipal tap water, including tap water used directly, beverages and foods prepared with municipal tap water either at home or in restaurants, and commercial beverages and processed foods prepared with municipal tap water. For a water fluoride level of 1 mg/L (1 ppm), estimated average exposures to fluoride from all sources range from about 0.03 mg/kg/day (mg of fluoride per kg of body weight per day) for adults and nursing infants to 0.09 mg/kg/day for non-nursing infants (especially infants fed formula prepared with fluoridated tap water). Note that these are estimated *average* exposures. For individuals with high tap water consumption (discussed by NRC 2006a), total fluoride exposures can exceed 0.1 mg/kg/day for some adults and may reach 0.2 mg/kg/day for some infants. In one of the few studies to evaluate individual intake of fluoride from all sources, Warren et al. (2008) report individual fluoride intakes (from all sources) in excess of 0.2 mg/kg/day for a few infants.

The NRC (2006a) identified several sizeable subgroups of the U.S. population that require special consideration due to above-average fluoride exposures, increased fluoride retention, or greater susceptibility to effects from fluoride exposures. For example, tap water consumption varies among individuals by more than a factor of 10, depending on age, activity level, and the presence of certain health conditions such as diabetes insipidus (NRC 2006a; see also Warren et al. 2008 for an example of estimated fluoride intakes for individual children at different ages). Infants have a very high fluid intake per unit body weight, such that infants whose formula is prepared with fluoridated tap water can receive very high fluoride exposures. The American Dental Association (2006) even suggests that fluoridated tap water not be used for preparation of infant formula. In its assessment of health risks posed or potentially posed to humans by fluoride exposure, OEHHA should consider the whole range of fluoride exposures as well as the various susceptible subpopulations.

OEHHA should also note that the U.S. Food and Drug Administration (FDA) considers fluoride in toothpaste to be a non-prescription drug (e.g., FDA 2002; 2006; undated-a; undated-b) and fluoride "supplements" (usually tablets or lozenges) to be prescription drugs (e.g., Medline Plus 2008.). However, many people consume more fluoride from other sources, primarily tap water (directly or indirectly), without any monitoring for either efficacy or side effects and without the "drug information" or warning labels generally provided for drugs.

3. Epidemiological data. To the cohort studies listed by OEHHA (2009c) should be added Grandjean and Olsen (2004), which is an update of the study by Grandjean et al. (1992). Also relevant here are time-trend studies described by Bundock et al. (1985) and Graham et al. (1987) and the earlier papers referenced therein. OEHHA should be aware that at least three courts in the U.S. have found fluoride to be carcinogenic to humans (described in detail by Graham and Morin 1999), based in part on the time-trend studies.

The case-control study by Bassin et al. (2006) is the only published study thus far to have looked at age-dependent exposure to fluoride. This study reported a significantly elevated risk of osteosarcoma in boys as a function of estimated age-specific fluoride intake. At the very least, this study indicates that similar studies of pediatric osteosarcoma that have not looked at age-dependent intake cannot be considered to show "no effect." Age- and sex-dependencies of cancer risk are biologically plausible and have been demonstrated for other types of carcinogenic exposures (e.g., radiation exposure; NRC 2006b).

While a few other studies (e.g., Gelberg et al. 1995) have looked at individual fluoride exposure (as opposed to group or ecologic measures of exposure), these have looked at total fluoride exposure until time of diagnosis or treatment. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time") cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure. Fluoride may exert a promotional effect, in addition to or instead of an initiation effect (NRC 2006a), in which case exposure during the "lag time" may be (or may continue to be) important, but this too could be obscured by looking only at a cumulative measure of fluoride exposure.

Douglass and Joshipura (2006) warn against putting too much stock in the results reported by Bassin et al. (2006), indicating that their own findings do not support Bassin's results. It should be noted that Douglass signed off on 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. In addition, the results promised by Douglass and Joshipura (2006) have not to date appeared in a peer-reviewed journal and cannot be evaluated by the scientific community. Douglass and Joshipura mention an analysis of the fluoride content of bone specimens from the osteosarcoma patients and a lack of association between bone fluoride concentration and excess risk of osteosarcoma; however, fluoride concentration in bones of diagnosed patients constitutes a measure of cumulative fluoride exposure as discussed above, and would not necessarily be expected to be correlated with the risk of osteosarcoma.

A very old finding in humans that may be of interest to OEHHA is 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, which was never investigated further, was considered "spurious," but no basis for this conclusion was provided (NRC 1977).

4. Animal carcinogenicity data. To the animal studies listed by OEHHA (2009c) should be the early studies of Taylor (1954) and Taylor and Taylor (1965). These studies are among the evidence used in the court cases, as discussed by Graham and Morin (1999).

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

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with an 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. Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the NTP study probably

corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely, the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas.

5. Other relevant data. On p. 2 of "Fluoride and Its Salts" (OEHHA 2009c), the review of genotoxicity by the National Research Council is stated as being in Chapter 6 of the NRC's 2006 report; this should be Chapter 10. Additional studies of genotoxicity or transformational activity not reviewed by the NRC but discussed by Graham and Morin (1999) include Herskowitz and Norton (1963), Mukherjee and Sobels (1968), Tsutsui et al. (1984a, 1984b), and Jones et al. (1988); these should also be reviewed by OEHHA.

It is important to note that a number of mammalian *in vitro* systems have shown dose-dependent cytogenetic or cell transformational effects from fluoride exposure. Several reports suggest an indirect or promotional mechanism, e.g., inhibition of DNA synthesis or repair enzymes, rather than a direct mutagenic effect (Lasne et al. 1988; Aardema et al. 1989; Aardema and Tsutsui 1995; Meng and Zhang 1997). It is worth noting that human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

Depending on the experimental system investigated, *in vitro* genotoxic effects have been reported at fluoride concentrations at or above about 5 mg/L (e.g., 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; see also Wu and Wu 1995; Meng et al. 1995; Meng and Zhang 1997). Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (0.07-0.09 mg/kg/day for an adult; NRC 2006a). Thus, kidney and bladder cells may potentially be exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported in vitro. In addition, cells in the vicinity of resorption sites in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006a) and thus are also at risk for genotoxic effects.

6. Reviews. Chapter 10 of the NRC report (NRC 2006a) also reviewed human and animal studies of carcinogenicity, in addition to genotoxicity studies, although the NRC's review did not include a number of the older studies mentioned above. The committee unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed." Referring to the animal studies, the committee also said that "the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans." The committee also discussed the limitations

of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk.

While the NRC committee did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the committee did not consider either “insufficient information” or “clearly not carcinogenic” to be applicable. The committee report (NRC 2006a) includes a discussion of how EPA establishes drinking water standards for known, probable, or possible carcinogens; such a discussion would not have been relevant had the committee not considered fluoride to be carcinogenic. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances. As mentioned, 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 2006a). OEHHA should recognize the lack of sensitivity of many studies to detect small effects. OEHHA should explore reasons why some studies have given negative results (e.g., age-specific exposure was not examined) and should try to evaluate factors that may affect the genotoxicity or carcinogenicity of fluoride in various systems. For example, are there situations (e.g., genetic factors or nutritional deficiencies) that cause individuals to be more susceptible in some situations than others, or cause some individuals to be more susceptible than others?

7. Other considerations. There has been a tendency in the U.S. to downplay or dismiss evidence for adverse health effects from fluoride exposure, due to the widespread belief that the benefits of fluoride exposure outweigh any risks. However, one major review of fluoride studies widely cited as showing the benefits of fluoride in reducing caries actually concluded that there are no high-quality studies showing benefits of fluoride exposure or that fluoride exposure reduces socioeconomic disparities in dental health (McDonagh et al. 2000; Wilson and Sheldon 2006; Cheng et al. 2007). Warren et al. (2008) found no significant difference in the mean individual fluoride exposures between children with and without caries experience. The only peer-reviewed paper that I have located 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). A number of sources (reviewed by NRC 2006a) indicate that any beneficial effect of fluoride on teeth is topical (e.g., from toothpaste), not from ingestion.

The small apparent benefits of fluoride exposure seen in some studies are likely due to the effect of delayed tooth eruption (e.g., Komárek et al. 2005)—permanent teeth erupt later in children in fluoridated areas, and thus have been exposed to a cariogenic environment for a shorter time than teeth of children of comparable age in unfluoridated areas. Although delayed tooth eruption as a result of fluoride exposure has been known since the 1940s (Short et al. 1944), this effect has not been considered in most studies reporting caries-reducing effects of fluoride.

Tickner and Coffin (2006) describe the importance of acting in a manner to protect public health, and discuss the application of the “precautionary principle”—“first do no harm”—to the issue of fluoride exposure. In that spirit, OEHHA should not simply assume a benefit of fluoride

exposure in assessing whether the California population is at risk for adverse health effects due to fluoride exposure. The burden should be on demonstrating safety to all members of the population, including members of sensitive or susceptible subgroups.

References

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

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.

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

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.

Bundock, J.B., D. Burk, J.R. Graham, and P.J. Morin. 1985. Fluorides, water fluoridation, cancer and genetic diseases. Science and Public Policy 12(1):36-46.

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.

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

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

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

FDA (U.S. Food and Drug Administration). 2002. Frequently asked questions to CEDR. Available at http://www.fda.gov/cder/about/faq/default.htm.

FDA (U.S. Food and Drug Administration). 2006. The New Over-the-Counter Medicine Label: Take a Look. Available at http://www.fda.gov/cder/consumerinfo/OTClabel.htm.

FDA (U.S. Food and Drug Administration). Undated-a. Medicines in My Home. Available at http://www.fda.gov/medsinmyhome/documents/MIMH_booklet_student.pdf/.

FDA (U.S. Food and Drug Administration). Undated-b. The New Over-the-Counter Medicine Label. Available at http://www.pueblo.gsa.gov/cic_text/health/new-otc-label/new-label.pdf.

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.

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.

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

Graham, J.R., D. Burk, and P. Morin. 1987. A current restatement and continuing reappraisal concerning demographic variables in American time-trend studies on water fluoridation and human cancer. Proceedings of the Pennsylvania Academy of Science 61:138-146.

Grandjean, P., and J.H. Olsen. 2004. Extended follow-up of cancer incidence in fluoride-exposed workers. J. National Cancer Institute 96(10):802-803.

Grandjean, P., J.H. Olsen, O.M. Jensen, and K. Juel. 1992. Cancer incidence and mortality in workers exposed to fluoride. J. National Cancer Institute 84(24):1903-1909.

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.

Herskowitz, I.H., and I.L. Norton. 1963. Increased incidence of melanotic tumors in two strains of Drosophila melanogaster following treatment with sodium fluoride. Genetics 48(2):307-310.

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: http://www.nteu280.org/Issues/Fluoride/629FINAL.htm or http://www.fluoridealert.org/HirzyTestimony.pdf.

Jones, C.A., M.F. Callaham, and E. Huberman. 1988. Sodium fluoride promotes morphological transformation of Syrian hamster embryo cells. Carcinogenesis 9(12):2279-2284.

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.

Medline Plus. 2008. Fluoride. U.S. National Library of Medicine and National Institutes of Health. Available at http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682727.html.

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

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.

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

Mukherjee, R.N., and F.H. Sobels. 1968. The effects of sodium fluoride and iodoacetamide on mutation induction by x-irradiation in mature spermatozoa of Drosophila. Mutation Research 6(2):217-225.

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

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

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

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). 2009a. Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/state_listing/prioritization_notices/prior030509.html.

OEHHA (Office of Environmental Health Hazard Assessment). 2009b. Prioritization of Chemicals for Carcinogen Identification Review: Proposed Chemicals for Committee

Consideration and Consultation. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/state_listing/prioritization_notices/pdf/Chemicals030509.pdf.

OEHHA (Office of Environmental Health Hazard Assessment). 2009c. Fluoride and Its Salts. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/state_listing/prioritization_notices/pdf/Fluoride.pdf.

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.

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.

Taylor, A. 1954. Sodium fluoride in the drinking water of mice. Dental Digest 60:170-172.

Taylor, A., and N.C. Taylor. 1965. Effect of sodium fluoride on tumor growth. Proceedings of the Society for Experimental Biology and Medicine 119:252-255.

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

Tsutsui, T., K. Ide, and H. Maizumi. 1984a. Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. Mutation Research 140:43-48.

Tsutsui, T., N. Suzuki, and M. Ohmori. 1984b. Sodium fluoride-induced morphological and neoplastic transformation, chromosome aberrations, sister chromatid exchanges, and unscheduled DNA synthesis in cultured Syrian hamster embryo cells. Cancer Research 44:938:941.

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. 2008. Considerations on optimal fluoride intake using dental fluorosis and dental caries outcomes—a longitudinal study. Journal of Public Health Dentistry (E-pub ahead of print, November 21, 2008).

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

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