



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

SEP - 6 2011

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Program
P.O. Box 4010 - MS-19B
1001 I Street, 19th Floor
Sacramento, California 95812-4010

Re: Selection of Fluoride for Consideration for Listing by the Carcinogen Identification Committee

Dear Ms. Oshita:

This letter concerns the California Office of Environmental Health Hazard Assessment's (OEHHA) selection of fluoride and its salts for consideration for listing by the Carcinogen Identification Committee under California's "Safe Drinking Water and Toxic Enforcement Act of 1986" (also known as Proposition 65). If fluoride were listed as a carcinogen under Proposition 65, it is our understanding that, when sold in the State of California, a product containing fluoride would have to bear a "clear and reasonable" warning stating that it contains a chemical known to the state to cause cancer. The Proposition 65 "safe harbor" warning for products containing fluoride would state, "WARNING: This product contains a chemical known to the State of California to cause cancer" (hereinafter "Proposition 65 cancer warning").

We are writing on behalf of the U.S. Food and Drug Administration (FDA or Agency) to inform you that we have determined that the available data do not support a conclusion that exposure to fluoride in FDA-regulated products causes cancer. Accordingly, a Proposition 65 cancer warning on the labeling of FDA-regulated products containing fluoride, including dental products and bottled water, would misbrand these products in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and, therefore, would be preempted.

1. FDA's Regulation of Products Containing Fluoride
 - a. Dental Products

FDA regulates many products containing fluoride, including over-the-counter (OTC) fluoride dentifrices (gels, pastes, and powders) and treatment gels and rinses for the prevention of tooth decay. Based on a review of both human and animal toxicology data by an independent expert advisory panel, FDA concluded in 1995 that fluoride is a safe and effective OTC anticaries drug when used in products that are formulated and labeled in conformance with the anticaries final monograph set forth in 21 CFR part 355 (60 FR 52474, October 6, 1995). Section 355.10 states the permissible concentrations and dosage forms for each of the anticaries active ingredients covered under the monograph.

b. Bottled Water

FDA regulates bottled water as a food. FDA's bottled water quality standard at 21 CFR 165.110(b)(4)(ii) specifies the level of fluoride that may be contained in bottled water. Fluoride can occur naturally in source waters used for bottled water. It may also be added by a bottled water manufacturer. There are different allowable levels for water to which fluoride has been added and water to which fluoride has not been added, as well as different allowable levels for imported and domestic products. Fluoride may be added within the limitations established in 21 CFR 165.110(b)(4)(ii) because FDA recognized that water with added fluoride may provide a benefit to consumers (i.e., prevention of tooth decay) and because bottled water may be used by some consumers as an alternative to community drinking water (60 FR 57076 at 57079, November 13, 1995). FDA also permits the following health claim for reduced risk of dental caries on bottled water products that meet certain criteria: "Drinking fluoridated water may reduce the risk of [dental caries or tooth decay]."¹

2. The Available Data Do Not Warrant the Conclusion That Fluoride Is a Carcinogen

Under the Safe Drinking Water Act, the U.S. Environmental Protection Agency (EPA) determines maximum contaminant levels (MCLs) and maximum contaminant level goals (MCLGs) for contaminants in drinking water. An MCLG is the level of a contaminant in drinking water below which there is no known or expected risk to health.² EPA established the MCLG (4 mg/L) for fluoride based on non-cancer health effects (40 CFR 141.51(b)). In determining the MCLG for fluoride, EPA concluded that there was "not adequate information to conclude that fluoride presents a cancer risk to humans" (50 FR 47142, November 14, 1985).³

At the request of EPA, in 1993 and 2006, the National Research Council (NRC) of the National Academies of Science conducted comprehensive reviews of the available data on fluoride's health effects. The 1993 NRC Report reviewed the available epidemiologic studies on the relationship between fluoride in drinking water and human cancer, as well as animal carcinogenicity and genotoxicity studies.⁴ The 1993 NRC Report concluded that the epidemiologic studies provided no credible evidence of an association between fluoride in drinking water and human cancer.⁵ It also reviewed the scientific literature on potential carcinogenic effects of fluoride in animals, placing particular emphasis on two conflicting studies. Although one study, conducted under the National Toxicology Program (NTP), showed

¹ See "Health Claim Notification for Fluoridated Water and Reduced Risk of Dental Caries" (<http://www.fda.gov/Food/LabelingNutrition/LabelClaims/FDAModernizationActFDAMAClaims/ucm073602.htm>).

² <http://water.epa.gov/drink/contaminants/index.cfm#1>.

³ As noted above, the EPA regulates maximum levels of fluoride in community water supplies under the Safe Drinking Water Act of 1974. In addition, the U.S. Department of Health and Human Services (HHS) provides recommendations for community water fluoridation to prevent tooth decay. HHS recently proposed a new recommended fluoridation level, 0.7 mg/l, to replace the previous recommended range of 0.7 to 1.2 mg/l, as the concentration that provides the best balance of protection from dental caries while limiting the risk of dental fluorosis (76 FR 2383, January 13, 2011). EPA is also reviewing its MCLG for fluoride to take into account additional non-cancer health effects, including dental fluorosis. There are several reasons for these changes, including the fact that Americans have access to more sources of fluoride than they did when water fluoridation was first introduced in the United States (http://www.cdc.gov/fluoridation/fact_sheets/cwf_qa.htm).

⁴ Subcommittee on Health Effects of Ingested Fluoride, National Research Council, Health Effects of Ingested Fluoride (1993) ("1993 NRC Report").

⁵ *Id.* at 109.

evidence of a dose-related increase in the incidence of osteosarcomas in male rats given high concentrations of fluoride,⁶ these results were not replicated in a second Procter & Gamble study, administering even higher doses of fluoride to male and female mice and rats.⁷ Furthermore, NTP concluded that under the conditions of its study, there was equivocal evidence of carcinogenic activity in male F344/N rats.⁸ The 1993 NRC report concluded that the available evidence did not support an association between fluoride exposure and an increased risk of cancer in humans. FDA has also reviewed these animal studies and has concluded that the osteosarcomas were not statistically significantly increased nor were they outside the historical control range. Thus, the studies do not support a concern about osteosarcoma because of fluoride exposure.

The NRC Committee on Fluoride in Drinking Water (the Committee) 2006 review of the health effects of fluoride focused on whether fluoride is associated with osteosarcoma.⁹ While the 2006 NRC Report found that the available evidence is tentative and mixed regarding an association between fluoride and bone cancer, it concluded that the evidence did not demonstrate that fluoride is a carcinogen. The Committee noted that although several new population studies evaluating cancer in relation to fluoride exposure are available, these studies had methodological limitations that make it difficult to draw conclusions.

OEHHA's March 2009 listing of relevant studies identified during the preliminary toxicological evaluation of fluoride and its salts includes the 2006 NRC Report, epidemiological studies, carcinogenicity studies in mice and rats, genotoxicity studies, and a review by the Agency for Toxic Substances and Disease Registry. The 2006 NRC Report appears to have reviewed the majority of the studies that are included in OEHHA's March 2009 listing, with the exception of a 2006 study by Bassin et al.¹⁰ The 2006 Bassin study presented findings from a subset of data from a larger Harvard School of Dental Medicine study by Douglass and Joshipura, which was ongoing at the time. The Bassin study purported to find an association between estimated childhood fluoride exposure from drinking water and osteosarcoma among young males, but not consistently among females. However, the authors of the Bassin study noted that it was only an "exploratory analysis" and cautioned that they were aware of additional results from other cases that did not replicate the findings from the cases in their study. The 2006 NRC Report also noted that the then-forthcoming Harvard School of Dental Medicine study by Douglass and Joshipura would be an important addition to the available fluoride database.¹¹ The findings of this study were subsequently published in a July 2011 paper by Kim et al.¹² The results of this more recent study do not replicate the findings of the Bassin study.

The Kim study measured bone fluoride levels in patients diagnosed with osteosarcoma and compared them with levels in patients with other types of tumors to determine the association

⁶ *Id.* at 116.

⁷ *Id.* at 11, 122.

⁸ In the NTP study, "equivocal evidence" pertains to a category of uncertain findings and is defined as a marginal increase of neoplasms that may be related to chemical administration.

⁹ Committee on Fluoride in Drinking Water, National Research Council, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards (2006)* ("2006 NRC Report").

¹⁰ Bassin et al., *Age-Specific Fluoride Exposure in Drinking Water and Osteosarcoma (United States)*, *Cancer Causes Control*, 17:421-428, 2006.

¹¹ 2006 NRC Report, *supra* note 9, at 10.

¹² Kim F, Hayes C, Williams P, Whitford G, Joshipura K, Hoover R, Douglass C. *An Assessment of Bone Fluoride and Osteosarcoma*. *J Dent Res* published online 28 July 2011.

between bone fluoride concentration and the incidence of osteosarcoma. Thus, unlike the Bassin study, where fluoride exposure was estimated, the Kim study compared actual levels of fluoride in the bone. The Kim study found there was no significant difference in the bone fluoride level between the group of patients diagnosed with osteosarcoma and the group of patients with other types of tumors (odds ratio = 1.33 with 95% confidence interval: 0.56 – 3.15). The results from this study do not support an association between osteosarcoma and fluoride. One of the potential limitations with this study, especially if risk is related to exposure at a specific time in a patient's life, was the significant age difference between the osteosarcoma group and the control group.

The July 8, 2011 OEHHA Hazard Identification Document (HID) on fluoride carcinogenicity to the Carcinogen Identification Committee cites additional mechanistic hypotheses for the occurrence of osteosarcoma in animals and humans. OEHHA concludes that there are multiple lines of evidence from mechanistic and other relevant data that appear to support the hypothesis that fluoride causes osteosarcoma. While data from these types of studies may suggest the plausibility of a link between fluoride and cancer, they often do not translate into the expected clinical outcome and are by themselves insufficient to determine causality. Conclusive data from animal and human studies on more clinically meaningful endpoints are required to make this determination.

3. A Proposition 65 Cancer Warning on FDA-Regulated Products Containing Fluoride Would Be Preempted Under Federal Law

As described above, FDA has determined that the available scientific data do not support a conclusion that exposure to fluoride from FDA-regulated products causes cancer. Accordingly, a requirement that such products be labeled with a Proposition 65 cancer warning because they contain fluoride would be false and misleading. Therefore, food and drug products that contain fluoride and are regulated by FDA would be misbranded in violation of the FD&C Act if the product labeling included the Proposition 65 cancer warning. See sections 301, 403(a), and 502(a) of the FD&C Act (21 U.S.C. sections 331, 343(a), and 352(a)). A Proposition 65 cancer warning for such products containing fluoride would therefore also be preempted under Federal law.

We would be happy to discuss these issues further.

Sincerely,

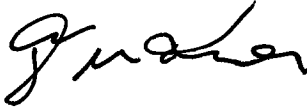


Janet Woodcock, M.D.

Director

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for

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