



founded 1881

Members of the Proposition 65
Carcinogen Identification Committee (CIC)

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Re: Hazard Identification Materials for Fluoride and Its Salts

Dear Members of the CIC and Ms. Oshita,

This letter is submitted on behalf of the Consumer Healthcare Products Association (CHPA).¹ The Office of Environmental Health Hazard Assessment (OEHHA) has provided you with Hazard Identification Materials (HIM) for fluoride and its salts (fluoride).² We applaud the HIM for its thoughtful and comprehensive review of the scientific literature, as well as its clarity and objectivity.

1. Overview

Because of fluoride's important role in promoting public health and preventing dental caries, the CIC's decision regarding fluoride has even greater significance than is usually the case. This letter sets forth the scientific and regulatory reasons that fluoride does not meet the Proposition 65 criteria for listing; specifically that fluoride has not "been clearly shown through scientifically valid testing according to generally accepted scientific principles to cause cancer." It also identifies and describes two important documents that were published shortly after the preparation of the HIM that further support the conclusion that fluoride does not cause cancer:

¹ CHPA, founded in 1881, is a member-based association representing the leading U.S. manufacturers and distributors of nonprescription, over-the-counter medicines and dietary supplements.

² OEHHA (2011) Evidence on the Carcinogenicity of Fluoride and Its Salts. (Hazard Identification Materials) July, p. 1-21.

- a recently published case-control epidemiologic study of fluoride and osteosarcoma (Kim et al., 2011)³
- a new review of fluoride by the EC Scientific Committee on Health and Environmental Risks (SCHER, 2011).⁴

2. New Epidemiologic Study of Fluoride and Osteosarcoma by Kim et al. (2011)

As background, Bassin et al. (2006) reported an elevated odds ratio in males with drinking water containing more than 1 ppm of fluoride in a hospital-based, case-control study of osteosarcoma in people less than 20 years of age. However, as noted in the HIM, Douglass and Joshipura (2006), epidemiologists who were involved in the Bassin study (but not listed as co-authors), advised readers “to be especially cautious when interpreting the findings of [the Bassin et al., 2006] paper for several reasons.” They stated that the Bassin et al. (2006) work “presents a partial view” of an ongoing study at Harvard University. They noted, “The authors themselves have already raised a red flag of caution in their final paragraph with the note that they are aware of additional findings from other incident cases that appear not to replicate the findings from the cases presented in their paper.” Finally, Douglass and Joshipura (2006) concluded: “Accordingly, readers are cautioned not to generalize and over-interpret the results of the Bassin et al. paper and to await the publication from the full study, before making conclusions, and especially before influencing any related policy decisions.”

Recently, another case-control hospital-based study conducted by Harvard researchers was published by Kim et al. (2011) (see footnote 3). Dr. Chester Douglass was the lead researcher and final author of this paper. The study design was approved by the National Institutes of Health’s National Cancer Institute (NCI), with funding provided by the National Institute of Environmental Health Sciences (NIEHS), National Institute of Dental and Craniofacial Research, and NCI. The purpose of the study was to

³ Kim FM, Hayes C, Williams PL, Whitford GM, Joshipura KJ, Hoover RN, Douglass CW, and the National Osteosarcoma Etiology Group (2011) An assessment of bone fluoride and osteosarcoma. *J Dental Research*. July 28 [Epub ahead of print]. <http://jdr.sagepub.com/content/early/2011/07/23/0022034511418828>

determine if bone fluoride levels were higher in individuals with osteosarcoma. Importantly, no significant association between bone fluoride levels and osteosarcoma risk was detected in this case-control study, based on controls with other tumor diagnoses.

Logistic regression of the incident cases of osteosarcoma (N=137) and tumor controls (N=51), adjusting for age and sex and potential confounders of osteosarcoma, was used to estimate odds ratios (OR) and 95% confidence intervals (CI). There was no significant difference in bone fluoride levels. The OR adjusted for age, gender, and a history for broken bones was 1.33 (95% CI: 0.56-3.15).

The Kim et al. study is the first epidemiologic study to employ actual bone fluoride concentration levels in the analysis. No association was found between fluoride levels and osteosarcoma risk. The direct measurement of bone fluoride concentration is a major advantage of the Kim et al. study as compared to estimating fluoride exposure based on levels in community drinking water. While the Kim et al. study is limited by the lack of age-matched controls, thereby resulting in controls that are significantly older than cases, the measurement of bone fluoride concentration as a direct indicator of fluoride exposure (as opposed to the indirect measures used by Bassin and others) represents the most accurate assessment of lifetime fluoride burden and shows no association between bone fluoride and osteosarcoma risk.

3. Recent Review of Fluoride by the EC Scientific Committee on Health and Environmental Risks (SCHER)

The European Commission's (EC) Scientific Committee on Health and Environmental Risks (SCHER) recently published a review entitled, "Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water" dated May 16, 2011. SCHER is an independent scientific committee that provides the EC with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment.

SCHER reviewed the human and animal carcinogenicity studies of fluoride, as well as the genotoxicity studies. Considering previous opinions from European Food Safety Authority (EFSA) and the EC

Scientific Committee on Consumer Safety (SCCS, formerly the SCCP), SCHER reviewed the newest information on the potential hazards of fluoride. SCHER's review of the epidemiologic studies included the Bassin et al. (2006) study, but not the recent Kim et al. (2011) study. Based on the available data, SCHER concluded:

“SCHER agrees that epidemiological studies do not indicate a clear link between fluoride in drinking water, and osteosarcoma and cancer in general. There is no evidence from animal studies to support the link, thus fluoride cannot be classified as carcinogenic.”⁵

“There is not sufficient evidence linking fluoride in the drinking water to the development of osteosarcoma.”⁶

4. Overall Assessment of the Scientific Evidence as Described in the HIM

These comments are directed to the following points:

- The HIM concludes that the current body of epidemiological evidence on the carcinogenicity of fluoride is considered inconclusive.
- The animal carcinogenicity studies of fluoride are insufficient to conclude that fluoride has been clearly shown to cause cancer.
- The genotoxicity studies and postulated mechanisms of action do not clearly show that fluoride causes cancer.
- The overall integration of the epidemiological and animal evidence, along with the genotoxicity data and the hypothetical mechanisms, does not support a conclusion that fluoride causes cancer.

⁵ Id., p. 17

⁶ Id., p. 39.

A. Statutory Standard

In reviewing the HIM and the additional data cited herein, the CIC must determine whether the Proposition 65 standard for listing has been met. To be listed by the CIC, fluoride must have “been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.”⁷ Anything less does not allow listing under this statute.

B. Conclusions

1. The HIM concludes that the current body of epidemiological evidence on the carcinogenicity of fluoride is considered inconclusive.

The HIM accurately concludes that the current body of epidemiological evidence (excluding the recent Kim et al. study) on the carcinogenicity of fluoride is inconclusive:

“Some positive findings in epidemiology studies, including reported increases in osteosarcomas in young males in an ecological study and in a hospital-based case-control study. However, the contribution of chance, bias, inappropriate analyses or confounding to these findings could not be ruled out. **Overall, the current body of epidemiologic evidence on the carcinogenicity of fluoride is considered inconclusive.**”⁸ [emphasis added]

Most of the numerous epidemiologic studies in the published scientific literature do not show a significant association between exposure to fluoride and the risk of osteosarcoma or cancer in general. OEHHA’s conclusion above was drawn even without the benefit of the results of the recent Kim et al. (2011) study, which showed no significant association between bone fluoride levels and osteosarcoma risk.

⁷ California Health and Safety Code § 25249.8.

⁸ OEHHA (2011) Evidence on the Carcinogenicity of Fluoride and Its Salts. (Hazard Identification Materials) July, p. 17.

Among the six case-control studies published to date, the sole positive case-control study was the Bassin et al. (2006) study, which reported “an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males but not consistently among females.”⁹ The authors of this study described their study as an “exploratory analysis” and noted several limitations of their study.¹⁰ Notably, the study’s “estimates of fluoride in drinking water at each residence did not include actual consumption by subjects and the study did not obtain biologic markers for fluoride exposure in bone.”¹¹ Of note is an earlier publication by Bassin et al. (2004), entitled “Problems in exposure assessment of fluoride in drinking water.”¹² This paper describes the limitations of using certain data sources to estimate fluoride in drinking water. Obviously, the level of fluoride in community drinking water, even when accurately determined, is not a direct measure of exposure to fluoride at the individual level, since it is necessary to know how much water from various sources (e.g. tap water, bottled water) is actually consumed.

Bassin et al. (2006) recommended that “future studies would benefit from the inclusion of biomarkers of fluoride exposure and assessment of potential gene-environmental interactions.”¹³ This statement is important in light of the fact that the subsequent case-control study by Kim et al. (2011) did measure fluoride levels in bone and did not find an association between fluoride exposure and osteosarcoma risk.

Summary of Epidemiological Studies

In summary, the epidemiological evidence is “inconclusive;” therefore, it follows that fluoride has not been clearly shown to cause cancer in humans.

2. The animal carcinogenicity studies of fluoride are insufficient to conclude that fluoride has been clearly shown to cause cancer.

⁹ Bassin EB, Wypij D, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States) Cancer Causes Control 17:421-428.

¹⁰ Id., p. 421, 425-7.

¹¹ Id., p. 426.

¹² Bassin EB, Mittleman MA, Wypij D, Joshipura K, Douglass CW (2004) Problems in exposure assessment of fluoride in drinking water. J Public Health Dentistry 64(1):45-49.

¹³ Bassin et al., (2006) p. 427.

The HIM notes some positive findings in a subset of animal carcinogenicity studies of fluoride in rats and mice:

“Some positive findings in animal carcinogenicity studies.

- Increased incidences of thyroid tumors and rare osteosarcomas in a two-year drinking water study in male F344/N rats, which were not replicated in a follow-up drinking water study.
- Increased incidences of benign osteomas in two-year diet studies in male and female CD-1 mice. The possible contribution of retroviral infection reported in the male and female mice to the development of osteomas could not be ruled out.”¹⁴

There are five carcinogenicity studies of fluoride in rodents: three in rats and two in mice. These are described below.

NTP (1990) Rat Study In the first of the three carcinogenicity studies of fluoride in rats, a positive trend test ($P=0.027$) for osteosarcoma was observed in male F344/N rats.¹⁵ But, there was no statistically significant increase in the incidence of osteosarcoma at any dose by pair-wise comparison to the control group. Based on these results, NTP concluded that there was “**equivocal evidence**” of carcinogenic activity in male rats under the conditions of the study.

In female rats, no significant increase in any tumor was observed. NTP concluded that there was “**no evidence**” of carcinogenic activity in female rats under the conditions of the study.

¹⁴ OEHHHA (2011) Evidence on the Carcinogenicity of Fluoride and Its Salts. (Hazard Identification Materials) July, p. 17.

¹⁵ NTP (1990) Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N rats and B6C3F1 mice (drinking water studies), Technical Report Series No. 393, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

The HIM notes a positive trend test for thyroid tumors (adenomas and carcinomas combined, but not carcinoma alone) in the male rats in this study. However, NTP did not consider these tumors to be related to fluoride exposure:

“Although there is a marginal numerical increase in follicular cell neoplasms in male rats receiving 175 ppm sodium fluoride, the incidence is not significantly greater than that in controls (Table A3). Moreover, the incidence of follicular cell neoplasms in the high-dose group is within the range of historical untreated controls (26/2,086, 1.2%, range 0-6%) (Table A4c), and the incidence of follicular cell hyperplasia is not increased in dosed rats (Table A5). Thus, the marginal increase in follicular cell neoplasms was not considered related to administration of the chemical.”¹⁶

NTP (1992) Rat Study Importantly, a second carcinogenicity study of fluoride in male F344/N rats was conducted by NTP.¹⁷ This study is important because no significant increase in osteosarcoma was reported, even though the male rats were exposed to a higher concentration of fluoride than in the earlier NTP study. This second NTP study has the power to call into question the “equivocal” result in the first NTP study.

This “supplemental” study was conducted by NTP in order to examine the effect of exposure to sodium fluoride on the incidence of bone tumors induced by ionizing radiation. Following exposure to ionizing radiation, one group of 50 male rats was administered drinking water containing 250 ppm sodium fluoride for two years while another group of 50 male rats received plain deionized water (without sodium fluoride). Two additional groups of 50 male rats (not exposed to radiation) received drinking water containing 250 ppm of sodium fluoride or plain deionized water. Exposure to irradiation, sodium

¹⁶ Id., p. 47.

¹⁷ NTP (1992) NTP Supplemental 2-Year Study of Sodium Fluoride in Male F344 Rats. Study No. C55221D. National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC. <http://ntp.niehs.nih.gov/index.cfm?objectid=16577B88-F1F6-975E-750961B2062D514E>

fluoride, or both irradiation and sodium fluoride was not associated with an increase in bone tumors or other neoplastic lesions.¹⁸

Maurer et al. (1990) Rat Study In a third carcinogenicity study of fluoride in rats, no incidence of preneoplastic or neoplastic lesions among Sprague-Dawley rats given fluoride in the diet for 99 weeks was significantly different from the control incidence.¹⁹ It is noteworthy that the highest dose in the Maurer et al. (1990) study was about three times the highest dose in the initial NTP study and there was fluoride-induced toxicity at this high level. Yet, no increase in the incidence of osteosarcoma or any other tumor type was observed in the Maurer et al. (1990) study. Thus, the “equivocal” result observed in male rats in the first NTP study was not confirmed in either the second NTP (1992) study or the Maurer et al. (1990) study, despite the fact that both of these studies used a higher dose than did the 1990 NTP study.

NTP (1990) Mouse Study No evidence of carcinogenicity was reported in a NTP study in B6C3F1 mice.²⁰ NTP concluded that there was “**no evidence**” of carcinogenic activity in male or female mice.

Maurer et al. (1993) Mouse Study In contrast to the NTP (1990) study in mice, Maurer et al. (1993) observed an increased incidence of osteoma in male and female CD-1 mice at the highest dose level.²¹ However the incidence of osteomas in all groups including controls was increased over that historically experienced at the lab and reported in the literature for CD-1 mice. It is important to note that osteoma is a *non-cancerous* bone tumor that may occur spontaneously or may be caused by retrovirus infection. The study authors concluded their “study was confounded by a retrovirus which contributed to the

¹⁸ The lack of an increase in tumors from irradiation was unexpected. The NTP attributed the lack of response to “the smaller size of the radiation field.” In this study, only a small area of the leg around the knee joint was irradiated; the rest of the leg and the entire body of the animal were totally shielded. The small size of the radiation field would not call into question the results of the animals exposed to sodium fluoride.

¹⁹ Maurer JK, Cheng MC, Boysen BG, Anderson RL (1990) Two-year carcinogenicity study of sodium fluoride in rats. J Natl Cancer Inst 82:1118-26.

²⁰ NTP (1990) Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N rats and B6C3F1 mice (drinking water studies), Technical Report Series No. 393, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

²¹ Maurer JK, Cheng MC, Boysen BG, Squire RA, Stradberg JD, Wesbrode SF, Seymour JL, Anderson RL (1993) Confounded carcinogenicity study of sodium fluoride in CD-1 mice. Reg Toxicol Pharmacol 18:154-68.

induction of the osteomas. Because the study was confounded, it cannot be considered a valid bioassay to be used for risk assessment.”

At the request of the National Research Council (NRC), the Armed Forces Institute of Pathology (AFIP) conducted an independent pathology review of the Maurer et al. (1993) study. The AFIP review concluded that the osteomas observed in the Maurer et al. (1993) study were more reminiscent of hyperplasia than neoplasia, and they were likely virally-induced. Further, AFIP concluded that “extrapolation to humans is impossible.” The AFIP review was summarized previously by OEHHA in a Public Health Goal (PHG) document for fluoride in drinking water:

“NRC asked the Armed Forces Institute of Pathology (AFIP) to evaluate the significance of the osteomas in the [Maurer et al., 1993] study (NRC, 1993). AFIP convened a committee of pathologists who reviewed the study and a sample of the histological slides. They concluded that the osteomas in question were not malignant and would not have progressed to a malignant state. They also stated that the presence of retroviral particles in the osteomas suggests that these viruses were involved in the induction of the osteomas (NRC, 1993).”²²

The HIM made similar points regarding the Maurer et al. (1993) study:

“Male CD-1 mice given fluoride in the diet showed a significant increase in osteomas (Maurer et al., 1993). Osteomas are benign bone tumors, usually occurring on the surface of the bone (Nilsson and Stanton, 1994). Osteomas do not progress to osteosarcomas or other types of malignant tumors, although there are rare reports in humans of progression to malignant osteoblastomas (Pieterse et al., 1983). Osteomas may occur spontaneously or they may be caused by retrovirus infection (Nilsson and Stanton, 1994). The type of retrovirus that has been shown to cause osteomas in mice is murine leukemia virus (Murray et al., 1986). The C-type

²² Office of Environmental Health Hazard Assessment (1997) Public Health Goal for Fluoride in Drinking Water. http://www.oeaha.ca.gov/water/phg/pdf/fluor_c.pdf

retrovirus particles identified by electron microscopy in the mice in the Maurer et al. 1993 studies are consistent with this type of virus.”²³

Summary of Animal Studies

In summary, the animal evidence of carcinogenicity is limited to:

1. a positive trend test for osteosarcoma in male rats only in the NTP (1990) study that could not be replicated in two subsequent carcinogenicity studies in rats administered a higher dose of fluoride, and
2. a significant increase in osteomas, a benign bone tumor most likely attributable to a virus (not fluoride), in mice that was not confirmed in a second mouse cancer bioassay conducted by NTP.

There was no statistically significant increase by pair-wise comparison in any malignant tumor in any carcinogenicity study of fluoride by NTP or by Maurer et al. in rats or mice. The NTP found “**equivocal evidence**” of carcinogenic activity of fluoride in male rats in one study only; NTP reported “**no evidence**” of carcinogenic activity of fluoride in male rats in a second NTP bioassay or in male mice, female mice, and female rats in NTP bioassays. Thus, the animal carcinogenicity studies of fluoride are insufficient to conclude that fluoride has been clearly shown to cause cancer.

3. The genotoxicity and mechanistic data do not clearly show that fluoride causes cancer.

The HIM postulates a number of “hypothetical mechanisms by which fluoride could be carcinogenic.”²⁴ These mechanisms include: genotoxicity, stimulation of cell division (mitogenesis), effects on thyroid function, and effects on immune function. While all of these hypotheses are considered potentially “biologically plausible,” none have proven to lead to fluoride-induced carcinogenicity. Further, there is

²³ OEHHA (2011) Evidence on the Carcinogenicity of Fluoride and Its Salts. (Hazard Identification Materials) July, p. 8.

²⁴ Id., p. 9.

insufficient evidence in epidemiological studies and in animal carcinogenicity studies that fluoride causes cancer. Theories regarding possible mechanisms of action are not sufficient to demonstrate that fluoride has been clearly shown to cause cancer, especially in the absence of convincing data that fluoride causes cancer in humans or animals.

While the HIM speculates on possible mechanisms of action, fluoride has not been demonstrated to cause cancer. Further, there are uncertainties associated with these postulated mechanisms of action. For example, there are uncertainties about genotoxicity as a postulated mechanism of action. One of the most extensive reviews of the toxicology and carcinogenicity of fluoride was conducted by the National Research Council Committee on Fluoride in Drinking Water (NRC, 2006).²⁵ This Committee was chaired by Dr. John Doull. The NRC Committee review provides a detailed review of the epidemiological studies, animal carcinogenicity bioassays, and genotoxicity studies of fluoride up until 2006. Chapter 10, entitled “Genotoxicity and Carcinogenicity” is particularly relevant. The NRC Committee summarized the genotoxicity data on fluoride as part of its review in 2006:

“Many assays have been performed to assess the genotoxicity of fluoride. Since the 1993 NRC review, the most significant additions to the database are *in vivo* assays in human populations and, to a lesser extent, *in vitro* assays with human cell lines and *in vivo* experiments with rodents. The results of the *in vivo* human studies are mixed. The results of *in vitro* tests are also conflicting and do not contribute significantly to the interpretation of the existing database. Evidence on the cytogenic effects of fluoride at environmental concentrations is contradictory.”²⁶

4. The overall integration of the epidemiological and animal carcinogenicity evidence, along with the genotoxicity and mechanistic data, does not clearly show that fluoride causes cancer.

²⁵ National Research Council (2006) *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* National Academies Press, Washington, DC.

²⁶ National Research Council (2006) *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* National Academies Press, Washington, DC, p. 9.

Overall, the integrated results of the epidemiological and animal carcinogenicity studies, together with the genotoxicity and mechanistic studies, do not demonstrate that fluoride causes cancer. Even without the results of the recent Kim et al. (2011) study, the HIM concludes the current body of epidemiological evidence on the carcinogenicity of fluoride is “inconclusive.” In five animal carcinogenicity studies of fluoride, there was no statistically significant increase (by pair-wise comparison) in any malignant tumor in any study. The NTP found “**equivocal evidence**” of carcinogenic activity of fluoride in male rats only in one study; NTP reported “**no evidence**” of carcinogenic activity of fluoride in male rats in a second NTP bioassay or in male mice, female mice, and female rats in NTP bioassays. And finally, the theories regarding plausible mechanisms of action whereby fluoride might cause cancer do not provide convincing evidence that fluoride has been clearly shown to cause cancer.

We hope the information provided herein will prove helpful. We would be pleased to respond to any questions from or provide additional information to OEHHA or the CIC members.

Sincerely,

Barbara A. Kochanowski, Ph.D.
Vice President, Regulatory & Scientific Affairs
Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006
202-249-3530