



founded 1881

May 5, 2009

Members of the Carcinogen Identification Committee

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Proposition 65 Implementation
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Re: Prioritization of Fluoride and its Salts

Dear Chairperson Mack and Members of the Carcinogen Identification Committee:

The Consumer Healthcare Products Association (CHPA) urges the Proposition 65 Carcinogen Identification Committee (CIC) to recommend a “no priority” for fluoride and its salts. CHPA, founded in 1881, is a member-based association representing the leading manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and nutritional supplements.

Summary

Fluoride and its salts should be assigned “no priority” for several reasons:

- The public health benefits of fluoride are well-recognized; drinking water fluoridation is strongly supported by many organizations, including the Centers for Disease Control and Prevention and the Surgeon General.
- While there are numerous studies of fluoride exposure and cancer in humans, there is no convincing evidence of a link between cancer and fluoride exposure. According to a recent review by the National Research Council Committee on Fluoride in Drinking Water (NRC, 2006), chaired by Dr. John Doull: “The human epidemiology study literature as a whole is still mixed and equivocal.”¹

¹ NRC (National Research Council) (2006) Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. p. 336.

- Carcinogenicity studies in animals (3 studies in rats and 2 studies in mice) do not provide significant evidence of carcinogenicity. According to the NRC (2006), “The collective data from the rodent fluoride toxicological studies do not present convincing evidence of an association between fluoride and increased occurrence of bone cancer in animals.”
- The evidence of genotoxicity is unpersuasive and contradictory.

Introduction and Background

On May 29, the CIC will consider the prioritization of 38 chemicals identified by OEHHA in the Notice entitled, “Prioritization of Chemicals for Carcinogen identification Committee Review: Proposed Chemicals for Committee Consideration and Consultation” dated March 2009 (the Notice). To identify these 38 chemicals, OEHHA submitted roughly half the existing “candidate chemicals” through two screens: an epidemiology data screen and animal data screen. OEHHA reported that 38 chemicals passed through at least one of these two screens.

On page 5-6 of the Notice, OEHHA provided a table (the Summary Table), which summarized the exposure characteristics and types of studies providing evidence of carcinogenicity for each of the 38 chemicals under consideration. While the table prepared by OEHHA indicates the types of studies available, it does not attempt to summarize the results of those studies.

OEHHA identified the scientific studies and review articles it found on the potential carcinogenicity of fluoride and its salts in a separate document (the OEHHA Fluoride Document). However, the OEHHA Fluoride Document simply described the general characteristics of each study, not whether the results were positive or negative.

The following sections of this submission briefly summarize the available evidence of carcinogenicity, following the general categories identified in the Summary Table. In addition, a second rat carcinogenicity study by NTP (1992), which was not identified in the OEHHA Fluoride Document, is summarized herein. When all of the evidence is considered, it is apparent that fluoride and its salts should not be a priority for further review. CHPA believes the available evidence supports a “no priority” recommendation for fluoride and its salts.

Exposure

In the Summary Table, OEHHA has correctly identified “widespread exposure” to fluoride and its salts. This is not surprising given the well-recognized public health benefits of fluoride. For example, the Centers for Disease Control and Prevention states:

“Since community water fluoridation began in 1945, it has been demonstrated to be a safe and cost-effective way to prevent tooth decay.”²

Since the 1950s, each U.S. Public Health Service Surgeon General has committed his or her support for community water fluoridation. Surgeon General Richard H. Carmona, M.D. states:

“As noted in *Oral Health in America: A Report of the Surgeon General*, community water fluoridation continues to be the most cost-effective, equitable and safe means to provide protection from tooth decay in a community. ... Water fluoridation is a powerful strategy in our efforts to eliminate differences in health among people and is consistent with my emphasis on the importance of prevention. ... I join previous Surgeons General in acknowledging the continuing public health role for community water fluoridation in enhancing the oral health of all Americans.”³

Many communities in California intentionally fluoridate their drinking water. Fluoridated toothpastes, mouthwashes and other dental treatments are other sources of intentional exposure. These exposures are widely regarded as beneficial uses of fluoride. In a 2007 Oral Health conference in Beijing, global experts agreed to the declaration: “fluoride toothpaste remains the most widespread and significant form of prevention of and protection against tooth decay used worldwide”⁴.

Human Data

The Summary Table correctly indicates there are both analytical and descriptive epidemiology studies of fluoride. The Background Document identifies a number of case-control studies of the general population and younger age groups, cohort studies, and ecological studies of fluoride and cancer. However, the epidemiological data does not show a clear association between fluoride exposure and cancer.

The National Research Council Committee on Fluoride in Drinking Water⁵ (NRC, 2006) reviewed the available epidemiological studies, and the NRC concluded:

² <http://www.cdc.gov/FLUORIDATION/benefits.htm>

³ http://www.cdc.gov/FLUORIDATION/fact_sheets/sg04.htm

⁴ World Health Organization, FDI World Dental Federation, International Association for Dental Research, Chinese Stomatological Association, editors. (2007) Beijing Declaration: Achieving dental health through fluoride in China and South East Asia. Conference on dental health through fluoride in China and South East Asia. Beijing, China.

⁵ Committee on Fluoride in Drinking Water: John Doull (Chair), University Kansas Medical Center, Kansas City; Kim Boekelheide, Brown University, Providence, RI; Barbara G. Farishian, Washington, DC; Robert L. Isaacson, Binghamton University, Binghamton, NY; Judith B. Klotz, University of Medicine and Dentistry of New Jersey, Piscataway, NJ; Jayanth V. Kumar, New York State Department of Health, Albany; Hardy Limeback, University of Toronto, Ontario, CANADA; Charles Poole, University of North Carolina at Chapel Hill, Chapel Hill; J. Edward Puzas, University of Rochester, Rochester, NY; Nu-May Ruby Reed, California Environmental Protection Agency, Sacramento, CA; Kathleen M. Thiessen, SENES Oak Ridge, Inc., Oak Ridge, TN; Thomas F. Webster, Boston University School of Public Health, Boston, MA; Susan N. J. Martel, (Project Director), National Research Council.

“The human epidemiology study literature as a whole is still mixed and equivocal.”⁶

The 2006 NRC Report Summary described the epidemiological evidence as tentative and mixed:

“Several new population studies investigating cancer in relation to fluoride exposure are now available. Some of those studies had significant methodological limitations that make it difficult to draw conclusions. Overall, the results were mixed, with some studies reporting a positive association and others no association. The committee concluded that the evidence to date is tentative and mixed as to whether fluoride has the potential to initiate or promote cancers, particularly of the bone.”⁷

Among the most recent studies was a case-control study of fluoride exposure and osteosarcoma incidence, using residential history for estimation of fluoride exposure. The complete study included two sets of cases with separate matched control groups. In an exploratory analysis using the first data set, Bassin et al. (2006) reported an association between childhood exposure to fluoride from drinking water and osteosarcoma in males <20 years old, but not females.⁸ However, preliminary analysis of the second set of cases by Douglass and Joshipura (2006) did not suggest an overall association between fluoride and osteosarcoma.⁹ These authors cautioned against over-interpretation of the Bassin et al. results, suggesting that conclusions await the publications from the full study.

Animal Data

The Summary Table characterized the animal data as “one study w/unusual incidence, site/type, age at onset.” However, in 1993, the NRC reviewed the available animal carcinogenicity studies of fluoride, which are exactly the same animal studies identified in the OEHHA Fluoride Document. In 1993, the NRC concluded:

“The collective data from the rodent fluoride toxicological studies do not present convincing evidence of an association between fluoride and increased occurrence of bone cancer in animals.”¹⁰

⁶ NRC (National Research Council) (2006) Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. p. 336.

⁷ NRC (National Research Council) (2006) Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. Report in Brief. March, 2006, p. 3.

⁸ Bassin EB, Wypij D, Davis RB, Mittleman, MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control*. 17:421-8.

⁹ Douglass CW, Joshipura K (2006) Caution needed in fluoride and osteosarcoma study. *Cancer Causes Control* 17:481-2.

¹⁰ National Research Council (1993) Health Effects of Ingested Fluoride. National Academy Press, Washington, D.C.

The evidence today is even less convincing that fluoride causes cancer in animals.

Rats

There are three carcinogenicity studies of fluoride in rats; two are identified in the OEHHA Fluoride Document. In the first study, NTP (1990) reported a positive dose-related increase in the trend ($p=0.027$) of osteosarcoma in male F344/N rats given fluoride in the drinking water. But, there was no statistically significant increase in the incidence of osteosarcoma at any dose by pairwise comparison to the control group. Based on these results, the NTP concluded that there was “equivocal evidence of carcinogenic activity” under the conditions of the study. The NRC (2006) characterized the findings in male rats in the NTP (1990) study as “borderline positive.”

Notably, two other carcinogenicity studies in rats, including a second study by NTP, did not demonstrate an increased incidence of osteosarcoma or any other tumor. The NTP conducted a second “supplemental” carcinogenicity of fluoride using the same strain of male rats¹¹. No significant increase in osteosarcoma was reported, even though the rats were exposed to a higher concentration of fluoride than in the earlier study.

In a third carcinogenicity study in rats (Maurer et al., 1990), no incidence of preneoplastic or neoplastic lesions was significantly different from that in controls among rats given fluoride in the diet. Thus, the “borderline positive” result in the first NTP rat study was not confirmed in two subsequent rat studies by NTP (1992) and Maurer et al. (1990).

Mice

There are two carcinogenicity studies of fluoride in mice. No evidence of carcinogenicity was reported in a NTP study in B6C3F1 mice. In comparison, Maurer et al. (1993) observed an increased incidence of osteoma (noncancerous bone tumors) in male and female CD-1 mice at the high dose level. However, a subsequent independent review of this study by the Armed Forces Institute of Pathology (AFIP) concluded that the osteomas were more reminiscent of hyperplasia than neoplasia, were likely virally-induced, and that “extrapolation to humans is impossible...”.NRC (1993) also concluded that their relevance to humans is questionable.

Genotoxicity

Numerous studies have been performed to assess the genotoxic potential of fluoride. These studies do not clearly demonstrate that fluoride is genotoxic. The NRC (2006) summarized the evidence of genotoxicity:

¹¹ National Toxicology Program (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.

“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 cytogenetic effects of fluoride at environmental concentrations is contradictory.”¹²

Thus, the fluoride genotoxicity data do not add to the weight of the evidence for carcinogenicity.

Conclusion

Fluoride and its salts represent a poor candidate for prioritization and hazard identification. The human and animal data are equivocal, and the genotoxicity data are conflicting. While human exposure to fluoride is widespread, there is a good reason: it provides a public health benefit. The well-recognized public health benefits should not be disregarded in favor of weak and equivocal evidence for risk. When all these factors are weighed, fluoride and its salts should be assigned “no priority.”

We appreciate the opportunity to submit these comments, and we look forward to participating and responding to your questions at the May 29, 2009 CIC meeting.

Sincerely,



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¹² NRC (2006), p. 9.