

Howard Pollick, BDS, MPH  
Clinical Professor  
Department of Preventive & Restorative Dental Sciences  
School of Dentistry, UCSF  
707 Parnassus Avenue  
San Francisco CA 94143-0758



Phone: 415-476-9872  
Fax: 415-476-0858  
email: [howard.pollick@ucsf.edu](mailto:howard.pollick@ucsf.edu)

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

Comments on the Report:  
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

[http://oehha.ca.gov/prop65/hazard\\_ident/pdf\\_zip/FLUORIDE070811.pdf](http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/FLUORIDE070811.pdf)

The review of the literature in this OEHHA Report provides the evidence needed for the Carcinogen Identification Committee to consider whether Fluoride and Its Salts should or should not be among the chemicals listed in Proposition 65.

Additional peer-reviewed evidence since the release of the Report provides further evidence that Fluoride and Its Salts should not be listed among the chemicals listed in Proposition 65.

Supplemental comments are added on subsequent pages.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "H. Pollick", is positioned below the text "Respectfully submitted,".

Howard Pollick, BDS, MPH

Chair, Fluoridation Advisory Council  
California Dental Association Foundation

It is commendable that the OEHHA Report (Evidence on the Carcinogenicity of Fluoride and Its Salts, OEHHA July 2011)<sup>1</sup> considered up-to-date peer-reviewed evidence on epidemiological, animal, *in vivo* and *in vitro* studies relevant to determining whether fluoride has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Statements are made in the OEHHA Report that demonstrate that fluoride and its salts do not clearly cause cancer. For example, on page 5 of the OEHHA Report: "...the current body of epidemiologic research on the carcinogenicity of fluoride remains inconclusive." Additionally, while there are "Some positive findings in animal carcinogenicity studies", the two positive studies mentioned found lack of replication of increased incidences of thyroid tumors and rare osteosarcomas and the "possible contribution of retroviral infection reported in the male and female mice to the development of osteomas could not be ruled out."

There have been two relevant publications that have become available since the OEHHA Report was made available. The first is the publication of an analysis on the second set of cases and controls from the Harvard study (Kim et al 2011<sup>2</sup>), of which the report by Bassin et al<sup>3</sup> was a part, that has provided evidence of a lack of association between fluoride in bone and osteosarcoma, details of which are presented below. The second is the report by the European "Scientific Committee on Health and Environmental Risks" (SCHER) dated 16 May, 2011: "Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water"<sup>4</sup>. The report 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."

### **Human Studies Do Not Clearly Show that Fluoride Causes Cancer**

With regard to the epidemiological studies cited in the OEHHA Report, statements are made about two human studies that reported increases in osteosarcomas in young males exposed to fluoride in drinking water. In the Summary of Evidence statement of the OEHHA Report, it is noted that of the "numerous epidemiological studies (ecological, cohort, and case-control) in human populations exposed to fluoride, primarily via drinking water", "Most studies are negative or inconclusive."

In describing the ecological study by Cohn (1992)<sup>5</sup>, that found an increased relative risk of osteosarcoma in young males (under age 20) living in fluoridated areas compared to areas without fluoridation, the OEHHA Report states: "Limitations of this study include the ecological design, drinking water fluoridation status based on residence at the time of diagnosis, small numbers of osteosarcomas observed (twelve in the exposed and eight in the unexposed populations), and limited reporting."

With regard to the ecologic study (Cohn 1992) included in the OEHHA Report, the York review on water fluoridation puts it into perspective.<sup>6</sup> With regard to osteosarcoma, the

York review found that of 12 studies of osteosarcoma, the direction of association between water fluoridation and osteosarcoma incidence or mortality was found to be positive (fewer cancers) in seven, negative (more cancers) in three, and two found no relationship. Of the six studies that presented variance data, one (Cohn 1992) found a statistically significant association between fluoridation and increased prevalence of osteosarcoma in males. This study, however, also had the lowest validity score, 2.5 out of 8. One study (Mahoney 1991) contributed four of the 12 analyses but did not provide variance data. Of eight analyses from the six studies of osteosarcoma and water fluoridation reporting variance data, none found statistically significant differences.

The York systematic review of water fluoridation considered 26 studies of the association of water fluoridation and all cancer. Eighteen of these studies were from the lowest level of evidence (level C) with the highest risk of bias. The York review concluded that there was no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers. Only two studies considered thyroid cancer and neither found a statistically significant association with water fluoridation. Overall, no clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer or all cancers was found.<sup>7</sup>

In the hospital-based case control study (Bassin et al. 2006<sup>3</sup>), the authors state that this is an exploratory analysis and make suggestions for how future studies can improve on the methods used. There is always difficulty with a case-control study in selecting an appropriate control group. In this study, the controls were from families that on average had a higher income and were generally from larger communities. There was a very small difference of less than a tenth of a milligram per liter between cases and controls in average estimated fluoride concentration of water. However the estimates rely on several assumptions. A case-control study can never find cause and effect but can suggest further areas of research. While osteosarcoma is a rare condition affecting about 6 people in a million under 24 years of age annually, there are about 180 million people in the US who have access to fluoridated water. There is no evidence that the incidence of osteosarcoma is increasing, yet the proportion of people with access to fluoridated water has increased.<sup>8,9</sup>

The OEHHA Report also cites Douglass and Joshipura (2006).<sup>10</sup> The following is a quote from that paper:

“The Harvard School of Dental Medicine study of fluoride and osteosarcoma has been a 15-year collaboration among NIEHS, NCI, NIDCR, and Harvard. Two sets of cases have been collected each with their own control groups. The study started in 1992. The first set of cases was recruited from existing cases between 1989 and 1992, and the second set of cases was recruited from new incident cases between 1993 and 2000. The Bassin et al paper reports age-specific results among only the cases from 1989 to 1992. We are also finding some positive associations between fluoride and osteosarcoma in the overall (not age-specific) analysis of the first set of cases. However, our preliminary findings from the overall analysis of the second set of cases (1993–2000) do not appear to replicate the overall findings from the first part of the study. Our findings currently being prepared for publication, do not

suggest an overall association between fluoride and osteosarcoma. This seems particularly important since the cases had been accrued essentially from the same hospitals within the same orthopedic departments with the same providers, and the same pathology departments making the diagnosis of the osteosarcoma and also using similar methods of fluoride exposure. In addition to fluoride intake history, many of the cases and controls that were accrued in the 1993–2000 time period agreed to provide bone specimens. The cases provided bone that was obtained proximal to the osteosarcoma lesion as well as from their contra lateral hip. The control group of non-osteosarcoma cancer patients provided bone specimens. Our preliminary analysis of the fluoride content of the bone specimens suggests that the fluoride level within the bone is not associated with excess risk of osteosarcoma. We are grateful to Dr. Bassin and her coauthors for mentioning at the end of their paper that we are not finding a positive association from the bone specimens in the second set of cases.” (end quote)

Following release of the OEHHA Report, there has been a publication of the “related series of osteosarcoma cases and controls”.<sup>2</sup> The Kim et al study determined if bone fluoride levels are higher in individuals with osteosarcoma. Incident cases of osteosarcoma (N = 137) and tumor controls (N = 51) were identified by orthopedic physicians, and segments of tumor-adjacent bone and iliac crest bone were analyzed for fluoride content. Logistic regression adjusted 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 between cases and controls. The OR adjusted for age, gender, and a history of broken bones was 1.33 (95% CI: 0.56-3.15). No significant association between bone fluoride levels and osteosarcoma risk was detected in the Kim et al case-control study, based on controls with other tumor diagnoses.

Limitations of the Kim et al study include disparities in age between the cases and controls. Additionally, Kim et al comment 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.” The mean age of the cases of osteosarcoma in Kim et al was 17.6 years with 27% (N=37) under 14 years of age. The mean age of the controls was 41.3 years with 17.7% (N=9) under 14 years. The low number of cases and controls under 14 years of age makes it impossible to statistically compare the findings from cases and controls for this age group that would be applicable to the larger population of osteosarcoma cases in young boys.

Whereas the Bassin et al study estimated fluoride intake based on residency histories and the reported or estimated fluoride concentration of drinking water, the Kim et al study measured fluoride accumulation from bone samples of the cases and controls. Each of these analyses contributes to the weight of the evidence. Further analyses of the data collected by the full multi-center study will make additional contributions, and the weight given to each will be affected by both limitations and whether they are confirmed by additional studies.

The weight of available evidence does not support the claim that fluoridation is causing osteosarcoma.

### **Animal Studies Do Not Clearly Show That Fluoride Causes Cancer**

With regard to animal studies, the Executive Summary of the OEHHA Report includes statements about studies showing increases in osteosarcomas or thyroid tumors, as well as studies showing no such increases.

Rodent studies have failed to confirm a relationship between fluoride intake, even at very high doses, and osteosarcoma, as noted in the summary of nine rodent bioassays performed by two laboratories in the 1990s. While stating in the OEHHA Report that “Rodents must be exposed to much higher levels of fluoride in diet or water than humans, in order to achieve the same bone fluoride levels”, nevertheless, the concentration of fluoride in drinking water and the doses of fluoride injected into the rodents were orders of magnitude higher than humans would be exposed to.

The 1990 NTP study<sup>11</sup> concluded: “Under the conditions of these 2-year dosed water studies, 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. Equivocal evidence is a category for uncertain findings defined as studies that are interpreted as showing a marginal increase of neoplasms that may be related to chemical administration. There was *no evidence of carcinogenic activity* in female F344/N rats receiving sodium fluoride at concentrations of 25, 100, or 175 ppm (11, 45, or 79 ppm fluoride) in drinking water for 2 years. There was *no evidence of carcinogenic activity* of sodium fluoride in male or female mice receiving sodium fluoride at concentrations of 25, 100, or 175 ppm in drinking water for 2 years.”

### **Other Studies Do Not Clearly Show That Fluoride Causes Cancer**

With regard to mutagenicity and clastogenicity, the Executive Summary of the OEHHA Report states that: “A mix of positive and negative results have been reported across test systems, with positive findings more often associated with higher concentrations of fluoride. In humans, positive findings of mutagenicity and clastogenicity have been reported in some studies of occupationally exposed workers and in some populations exposed to elevated levels of fluoride in drinking water.”

The OEHHA Report refers to malignant transformation in the Syrian hamster embryo (SHE) cell transformation assay in tests conducted in three different laboratories, as well as fluoride induced malignant transformation in the BALB/c 3T3 (mouse) promotion assay, but not in the BALB/c 3T3 cell standard focus assay. Other studies using the SHE cell transformation assay have found that fluoride did not act as a carcinogen without the presence of a known carcinogen.<sup>12</sup> The Report later suggests that the SHE cell transformation assay “continues to be considered a valid test for use in carcinogen testing” in spite of the statement from the 2006 NRC report<sup>13</sup> that “this assay is not a reliable predictor of effects in other animals or humans”.

When considering the hierarchy of assays, data from the SHE cell transformation *in vitro* screening assay may be useful to predict the outcome of a bioassay but do not take precedence over actual rodent bioassay data. Such data cannot be useful to confirm or negate findings from a rodent bioassay, or resolve questionable findings.

The statement in the OEHHA Report on thyroid and parathyroid effects of fluoride is only suggestive regarding the influence on bone growth, but not on carcinogenicity. “Fluoride affects thyroid and parathyroid function in humans and animals, elevating thyroid stimulating hormone levels, altering levels of the thyroid hormones T3 and T4, and increasing levels of parathyroid hormone and calcitonin. These changes can affect the rate of formation of bone tissue and the overall rate of bone growth.”<sup>1</sup>

The 1990 NTP study concluded that “...follicular cell neoplasms of the thyroid are not considered related to sodium fluoride administration.”<sup>14</sup>

The statement of the OEHHA Report on cellular immune response effects of fluoride is only suggestive regarding the influence on inflammation, which may play a role in carcinogenesis. “Fluoride can either stimulate or inhibit cellular immune responses in humans, rats, and mice. Decreases in cellular immune response may lead to a reduction in the ability of the immune system to identify and remove cancerous cells (*i.e.*, immune surveillance). Increases in cellular immune response may lead to inflammation, which may play a role in carcinogenesis.”

The statement of the OEHHA Report on multiple lines of evidence from mechanistic and other relevant data effects of fluoride is only suggestive regarding several hypotheses on carcinogenicity. “Taken together, these multiple lines of evidence from mechanistic and other relevant data appear to support several plausible hypotheses: that fluoride is incorporated into bones (especially rapidly growing bones), where it can i) stimulate cell division of osteoblasts via direct mitogenicity and indirectly via effects on thyroid function and parathyroid function; ii) induce genetic changes; iii) induce other cellular changes leading to malignant transformation, and iv) alter cellular immune response, resulting in increased inflammation and/or reduced immune surveillance, thereby increasing the risk of development of osteosarcomas.”

The statement on genotoxicity effects of fluoride from the NRC (2006) report on the *in vitro* evidence for genotoxicity of fluoride is described as inconsistent and inconclusive.<sup>13</sup> The OEHHA Report however takes a position contrary to the NRC report on the relevance to the practical genotoxic potential in humans, suggesting that occupational or environmental high exposure should be considered.

The OEHHA Report states: “The NRC (2006) report described the *in vitro* evidence for genotoxicity of fluoride as inconsistent and inconclusive, and the *in vivo* human studies as of questionable relevance to the “practical genotoxic potential in humans,” because these studies involved populations exposed to very large amounts of fluoride.”

Several statements are made in the OEHHA Report citing Martin et al 2011 regarding genotoxicity and cell transformation. However, it must be noted that nowhere in the Martin 13-page paper with 174 references is fluoride mentioned.<sup>15</sup>

The OEHHA Report states: “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.” This statement by the OEHHA 2011 Report authors should be qualified, since it is the inter- and intra-cellular low fluoride concentration that is the relevant variable in cellular exposure, and not the high fluoride concentration of total bone.

The OEHHA Report states: “The overall conclusions of the 2006 NRC report regarding the genotoxicity of fluoride, based on data from model systems (*in vivo* and *in vitro*) and on human occupational and ecological studies, is that the results are inconsistent and do not provide a basis for any firm conclusions about the potential of fluoride to be genotoxic in humans.”

The OEHHA Report states: “Fluoride increased the frequency of structural and numerical chromosomal aberrations, and was positive in the comet assay in human peripheral blood lymphocytes (Tiwari and Rao, 2010).” “Fluoride increased the frequency of sister chromatid exchanges and was positive in the comet assay in cultured human lymphocytes (Pant and Rao, 2010).”

However, it should be noted that in Tiwari and Rao,<sup>16</sup> and Pant and Rao,<sup>17</sup> human blood lymphocytes were exposed to a fluoride concentration of 34  $\mu\text{M}$  (micromolar) sodium fluoride (NaF), which is equivalent to 0.65 mg/L or parts per million (ppm) of fluoride (F) for 24 hours.

The normal range of fluoride in blood is 0.02 – 0.04 ppm F. Thus the concentration of fluoride used in this experiment was 15-30 times higher than normal. Where the drinking water contains 1 ppm fluoride, the plasma level is about 1  $\mu\text{M}$  (micromolar).<sup>18</sup>

In Podder et al (2011)<sup>19</sup> mice were subjected to drinking water containing 15 mg/L (ppm) for 30 days. In Podder et al (2010)<sup>20</sup> NaF was injected intraperitoneally into male Swiss-albino mice. Doses of NaF were selected ranging from 2.5 to 30 mg/kg b.w. based on the LD50 value (50.2 mg/kg b.w.) of NaF (Pillai et al., 1988). The recommended Tolerable Upper Limit of fluoride for humans is 0.1 mg/kg bw.<sup>21</sup> When humans or animals orally consume fluoride, it is diluted in the body. When injected into mice in experiments, at a concentration of 2.5 – 30 mg/kg bw, this is a comparison dose of at 25 – 300 times the daily dose. This experiment was intentionally designed to create NaF-induced genotoxicity with such high doses.

While many statements are made in the OEHHA Report that suggest mechanisms whereby fluoride *may* be implicated in carcinogenesis, there are no statements that state it categorically.

### **No Other Authoritative Body Has Concluded that Fluoride is a Carcinogen**

None of the agencies listed in the OEHHA Report have indicated that fluoride is a carcinogen. The OEHHA Report states: "Fluoride was reviewed by the U.S. EPA (2007) and classified in Group D (inadequate evidence of carcinogenicity)." The OEHHA Report also states: "Fluoride has not been classified as to its potential carcinogenicity by the U.S. Food and Drug Administration, NTP, the National Institute for Occupational Safety and Health, or IARC." The International Agency for Research on Cancer (IARC) 1987 review of evidence for carcinogenicity of fluoride, inorganic fluorides used in drinking water were found "not classifiable as to carcinogenicity to humans".<sup>22</sup>

There is a statement in the 1990 NTP study that cites the IARC findings: "The International Agency for Research on Cancer (IARC) has concluded that none of the studies reported up to their initial review in February 1981 had "provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality"; this conclusion was reaffirmed in a subsequent review in March 1987."<sup>11</sup>

With regard to other agencies not listed in the OEHHA Report, the European "Scientific Committee on Health and Environmental Risks" (SCHER) released a report dated 16 May, 2011: "Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water".<sup>4</sup> The report 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."

Additionally, the American Conference of Governmental Industrial Hygienists lists fluoride as A4; Not classifiable as a human carcinogen.<sup>23</sup>

The OEHHA Report suggests several plausible hypotheses whereby fluoride could increase the risk of osteosarcoma development. However, they remain as hypotheses.

### **Conclusions:**

The OEHHA Report states: "Overall, the current body of epidemiologic evidence on the carcinogenicity of fluoride is considered inconclusive."

While there are "Some positive findings in animal carcinogenicity studies", the two positive studies mentioned found lack of replication of increased incidences of thyroid tumors and rare osteosarcomas and the "possible contribution of retroviral infection reported in the male and female mice to the development of osteomas could not be ruled out."

With regard to “Mechanistic and other relevant data considerations”, no definitive statements are made about the carcinogenicity of fluoride. *In vitro* mutagenicity studies in bacteria and animal cells yielded some positive and some negative results. *In vitro* clastogenicity studies in animal and human cells yielded some positive and some negative results. *In vivo* mutagenicity and clastogenicity studies in humans and animals yielded some positive and some negative results.

In summary, the review of the literature in this OEHHA Report provides the evidence needed for the Carcinogen Identification Committee to conclude that fluoride is not a carcinogen and should not be among the chemicals listed in Proposition 65.

Additional peer-reviewed evidence since the release of the Report provides further evidence that Fluoride and Its Salts should not be listed among the chemicals listed in Proposition 65.

While that concludes these comments on the OEHHA Report, other studies not included in the OEHHA Report may be introduced by others as comments. Included here is a review of an article that does not meet generally accepted scientific standards.

[Sandhu R, Lal H, Kundu ZS, Kharb S. Serum Fluoride and Sialic Acid Levels in Osteosarcoma. \*Biol Trace Elem Res\*. 2009 Apr 24. \[Epub ahead of print\]. Accessed at <http://www.springerlink.com/content/w4587835r8812283/fulltext.pdf>](http://www.springerlink.com/content/w4587835r8812283/fulltext.pdf)

This study found increased serum fluoride in osteosarcoma cases compared to controls with other bone tumor or musculoskeletal pain. While the authors conclude a role of fluoride in osteosarcoma, they did not consider the possibility that there is increased bone turnover in osteosarcoma cases with fluoride release from bone.

It appears that the paper by Sandhu was submitted on April 6th and accepted for publication on April 13th without a review. The Sandhu article draws inappropriate conclusions. This is a low quality case control study with sketchy details of the methods. This probably has the shortest methods section of any case-control study published. The authors do not describe how the cases and controls were selected, how fluoride level was measured or the type of medication used. Only fasting serum fluoride concentration is a good marker of long term exposure to fluoride and bone concentration. Otherwise, it is not a marker. Statements like this "A positive correlation was observed between rise in sialic acid levels and fluoride levels, although the difference was not statistically significant ( $r=0.00017$ ,  $p<0.05$ )" perplex me. It appears that the authors do not realize that the increased fluoride level could have occurred as a result of osteosarcoma. (Jay Kumar, Personal Communication).

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