May 5, 2009

Cynthia Oshita  
Office of Environmental Health Hazard Assessment  
Proposition 65 Implementation  
P.O. Box 4010/1001 I Street, 19th floor  
Sacramento, CA 95812-4010

RE: Fluoride and its Salts - Prioritization of Chemicals for Carcinogen Identification Committee  
Review: Proposed Chemicals for Committee Consideration and Consultation, 2009

Dear Ms. Oshita:

The California Dental Association (CDA) urges members of OEHHA’s Carcinogen Identification Committee to place fluoride and its salts in the priority ranking of “no priority” when it reviews the 38 chemicals before it for consideration on May 29, 2009. While CDA strongly believes that solid science should prevail in evaluating the use of any dental treatment, based on the most current and reputable science we do not believe that moving fluoride to a higher review level is warranted at this time.

This recommendation is made on the basis of (1) the National Resource Council review of scientific literature on carcinogenicity of fluoride (Fluoride in Drinking Water – A Scientific Review of EPA’S Standards, NRC, 2006) and (2) analysis of research conducted by Bassin et al. (2006).

The National Resource Council report is the most recent review available of scientific literature on the health effects of fluoride exposure. The following quote is from the executive summary of the National Resource Council review:

“On the basis of the committee’s collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro), the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed. Assessing whether fluoride constitutes a risk factor for osteosarcoma is complicated by the rarity of the disease and the difficulty of characterizing biologic dose because of the ubiquity of population exposure to fluoride and the difficulty of acquiring bone samples in nonaffected individuals.”

The executive summary also points to the potential contributions of a large hospital-based case-control study of osteosarcoma and fluoride exposure, which when completed will add significantly to existing data and help guide the focus of future research in this area.
The study conducted at the Harvard School of Dental Medicine, on which the Bassin study (Age-specific fluoride exposure in drinking water and osteosarcoma, Cancer Causes Control, 2006) was expected to be published in 2006. Instead, the study’s chief investigator, Chester W. Douglass, DMD, PhD., wrote in the same journal issue (Caution needed in fluoride and osteosarcoma study, Cancer Causes Control, 2006) that researchers were delaying publication of all major findings. Essentially, they have been unable to find replications of earlier findings and continue to pursue and analyze data until they find replication or lack of replication.

Dr. Douglass’ letter includes background information on the Harvard study and also a cautionary statement regarding the Bassin article:

“We would like to advise the readers to be especially cautious when interpreting the findings of this paper for several reasons. The authors themselves have already raised a 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.”

We are also providing you with a detailed response from Howard Pollick, BDS, MPH, Clinical Professor in the Department of Preventive and Restorative Dental Services at the School of Dentistry at the University of California, San Francisco. Dr. Pollick has been on the faculty at UCSF since 1981, is a diplomate of the American Board of Dental Public Health, and is a widely respected and sought-after expert on fluoridation for the American Dental Association. We believe that Dr. Pollick’s analysis clearly supports keeping fluoride and its salts in the “no priority” category.

Thank you for your consideration.

Sincerely,

Gayle Mathe
Manager, Policy Development

Attachment
In the International Agency for Research on Cancer (IARC) 1987 review, inorganic fluorides used in drinking water were “not classifiable as to carcinogenicity to humans”.


International Agency for Research on Cancer (IARC) - Summaries & Evaluations. FLUORIDES (INORGANIC, USED IN DRINKING-WATER) (Group 3). Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans. This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

In reviewing the evidence from the citations selected by the California Office of Environmental Health Hazard Assessment (OEHHA) (March 2009), a clear distinction needs to be made regarding the usual dose or concentration of fluoride from water fluoridation and/or dental products and its effect on humans or animals (compared to cells where the normal fluoride exposure is in the order of 1/100th of the concentration), and the high dose or concentration of fluoride that workers may be exposed to in industrial processes or animals may be intentionally exposed to during experiments.

When taken separately and as a whole, the references cited indicate that inorganic fluorides at the levels that humans are commonly exposed to are “not classifiable as to carcinogenicity to humans”.

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What follows are the abstracts, quotes and comments related to the references cited in: Office of Environmental Health Hazard Assessment. March 2009 Chemical for CIC Consultation: Fluoride and Its Salts

Epidemiological data
• Case-control studies of younger age groups

o U.S. hospital-based case-control study of fluoride exposure and osteosarcoma in persons <20 years of age: Bassin et al. (2006).

Age-specific fluoride exposure in drinking water and osteosarcoma (United States).
Bassin EB, Wypij D, Davis RB, Mittleman MA. Cancer Causes Control. 2006 May;17(4):421-8

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.

Reference:
Increasing incidence of childhood cancer: report of 20 years experience from the greater Delaware Valley Pediatric Tumor Registry.
Bunin GR, Feuer EJ, Witman PA, Meadows AT.

An additional relevant reference is:
Caution needed in fluoride and osteosarcoma study.
Douglass CW, Joshipura K.
Cancer Causes Control. 2006 May;17(4):481-2.
Quote: “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)


Fluoride exposure and childhood osteosarcoma: a case-control study.
Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R.
Quote: “A strength of this study was the relatively large sample size (122 case-control pairs for the parents’ data set and 64 case-control pairs for the subjects’ data set) compared with prior studies that examined individual fluoride exposures from drinking water. Another advantage of this study was the inclusion of exposures to fluoride from sources other than drinking water.” (end quote)
Quote: “In conclusion, this study provides no support for the hypothesis that fluoride exposure increases the risk for osteosarcoma. It contributes to the body of evidence that indicates that the public can continue to enjoy the dental health benefits of fluoride with no associated major risks.” (end quote)
A case-control study of osteosarcoma in young persons.
Operskalski EA, Preston-Martin S, Henderson BE, Visscher BR.
Am J Epidemiol. 1987 Jul;126(1):118-26
Quote: “There was no suggestion of an association with exposure to...fluorides...” (end quote)

The CDC has posted on their website the CDC Statement on Water Fluoridation and Osteosarcoma.
http://www.cdc.gov/FLUORIDATION/SAFETY/OSTEOSARCOMA.HTM

CDC Statement on Water Fluoridation and Osteosarcoma

Osteosarcoma is a type of rare bone cancer. About 400 children and adolescents in the United States are diagnosed each year, approximately 250 of whom are males. An observed association between exposure to fluoride in drinking water and the incidence (new cases) of osteosarcoma in young males has been reported in a paper entitled Age-specific Fluoride Exposure in Drinking Water and Osteosarcoma (United States) (Bassin et al., 2006). No apparent association was observed in females. This research, which the author describes as an exploratory analysis, adds to the scientific knowledge base on this topic. The author acknowledges that this study has limitations and further research is required to confirm or refute this observation.

This paper is based on the analysis of an initial set of cases from a 15-year effort to study fluoride and osteosarcoma by the Harvard School of Dental Medicine and collaborating organizations. The principal investigator for the overall study cautions against over interpreting or generalizing the results of the Bassin analysis, stressing that preliminary analysis of a second set of cases does not appear to replicate the findings (Douglass et al., 2006). Publications from the forthcoming analyses are expected to provide further information as to whether and to what extent an association may exist between osteosarcoma and exposure to fluoride.

A number of studies regarding water fluoridation and osteosarcoma have been published in the past. At this time, the weight of the scientific evidence, as assessed by independent committees of experts, comprehensive systematic reviews, and review of the findings of individual studies does not support an association between water fluoridated at levels optimal for oral health and the risk for cancer, including osteosarcoma. In a report issued in March 2006, Fluoride in Drinking Water: A Scientific Review of EPA’s Standard, the National Research Council (NRC, 2006) considered all available evidence on fluoride and osteosarcoma, including pre-publication data from the analysis by Dr. Bassin. The NRC Committee found the overall evidence on osteosarcoma to be tentative and mixed, and no recommendations were made related to this health concern for revising current allowable fluoride levels in drinking water. The report stated that the results of the larger Harvard study, once published, may provide an important and useful addition to the weight of scientific evidence regarding this condition.

The following is an extract from:
Concerns about water fluoridation, IQ, and osteosarcoma lack credible evidence.
Pollick HF.
Quote: “With regard to osteosarcoma, the York review on water fluoridation (McDonagh MS, Whiting PF, Wilson PM, et al. Systematic review of water fluoridation. BMJ 2000;321(7265):855-9) 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.” (end quote)

• Case-control studies of general populations
  o Case-control study of fluoridated water and osteosarcoma in Massachusetts: McGuire et al. (1991)

  Is there a link between fluoridated water and osteosarcoma?
  McGuire SM, Vanable ED, McGuire MH, Buckwalter JA, Douglass CW.
  Abstract: “To test the hypothesis that fluoride is a risk factor for osteosarcoma, a case control study compared the complete residential fluoride histories of osteosarcoma patients with matched hospital-based controls. Fluoridation was not found to be a risk factor for osteosarcoma in the study population. The trend in the data from this small sample study suggests the hypothesis that a protective effect may exist against the formation of osteosarcoma for individuals consuming fluoridated water.”

• Cohort studies

  Mortality in aluminum reduction plant workers.
  Milham S Jr.
  Abstract: “Mortality in workers at a northwestern United States prebake-type aluminum reduction plant was examined in a historical prospective (cohort) study. Although the standardized mortality ratio (SMR) for all causes of death was low (86), lung cancer (SMR 117), pancreatic cancer (SMR 180), lymphatic and hematopoietic cancers (SMR 184), fatal benign tumors of the brain (SMR 391), and pulmonary emphysema (SMR 204) showed excess deaths. Analysis of mortality by job-exposure category, duration of employment and latency suggests that some of the lymphatic and hematopoietic cancers (especially malignant lymphoma), lung cancers and pulmonary emphysema may be of occupational origin in this worker population.”

  o Cancer mortality study among aluminum reduction plant workers exposed to hydrogen fluoride: Rockette and Arena (1983)

  Mortality studies of aluminum reduction plant workers: potroom and carbon department.
  Rockette HE, Arena VC.
  Abstract: “The purpose of this study was to investigate mortality patterns of aluminum reduction plant workers. A cohort was formed of 21,829 workers with five or more years employment in 14 reduction plants. Progress of the study was reported quarterly to a Tripartite Committee consisting of representatives from labor, management and government. Although the results of other studies relative to an excess of lung cancer in aluminum workers were not confirmed, there were indications of a higher than expected mortality in pancreatic cancer, lymphohematopoietic cancers, genitourinary cancer, nonmalignant respiratory disease and benign and unspecified neoplasms.”

  o Cancer mortality study among cryolite processing plant workers exposed to fluoride: Grandjean et al. (1992)

  Cancer incidence and mortality in workers exposed to fluoride.
  Grandjean P, Olsen JH, Jensen OM, Juel K.
  Abstract: “BACKGROUND: Although a recent bioassay showed increased frequency of bone cancer in rats with high oral intake of fluoride, the data are reported as equivocal evidence of carcinogenicity. In humans, occupational fluoride exposure may cause skeletal fluorosis, and our earlier follow-up of fluoride-exposed workers showed increased incidence of respiratory cancers. PURPOSE: To further evaluate occupational fluoride exposure as a carcinogenic risk factor, we extended by approximately one decade the follow-up of a
cohort of 425 men and 97 women employed for at least 6 months in the period 1924-1961 at the Copenhagen cryolite processing plant. Cryolite ore contains about 50% fluoride. METHODS: Cancer mortality was determined for the period 1941-1989, and incidence for 1943-1987. For comparison, we used national mortality rates and cancer incidence rates for the Copenhagen area. RESULTS: Among the men, 300 deaths occurred; 223 were expected. Respiratory (lung and laryngeal) cancers and violent death were responsible for most of this excess; rates for mortality from cardiovascular disease were close to the rates expected. Of the 423 male workers, 119 developed cancers; 103.6 were expected. There was excess incidence of cancers of the lungs (35 men; standard incidence ratio [SIR] = 1.35), larynx (5 men; SIR = 2.29), and urinary bladder (17 men; SIR = 1.84). Maximum incidence occurred after 10-19 years of employment, but otherwise, no stable relationship between cancer incidence and duration of employment was observed. The incidence of respiratory and urinary cancers was particularly high in men less than 35 years old at first employment. Cancers in female workers were too few to allow detailed evaluation. CONCLUSIONS: The increased incidence of respiratory cancers suggests that cigarette smoking was frequent in this cohort, despite the unremarkable cardiovascular mortality, but the disproportionate increase in the incidence of bladder cancer is difficult to explain by smoking habits alone. Because this industrial cohort was exposed to high concentrations of fluoride dust, heavy respiratory exposure to fluoride may have contributed to the increased cancer risk. If these workers inhaled a carcinogenic substance partly excreted in the urine, an increased incidence of respiratory and bladder cancers would not be inconceivable. IMPLICATION: The potential role of fluoride as a cause of bladder cancer needs to be explored.

• Ecological studies limited to younger age groups

  o Report from the New Jersey Department of Health examining the relationship between drinking water fluoridation and osteosarcomas in young men: Cohn (1992)  [The study has not been published in a peer reviewed journal]

  Quote (Page 15: Conclusions and Recommendations): “This exploratory study suggested an association between the fluoridation of drinking water and the incidence of childhood osteosarcoma among males and corroborates the results of a similar type of study conducted nationally by the National Cancer Institute. Since interviews were not conducted in either study, detailed exposure and residency information was not available. Therefore, even taking both studies together, there is insufficient basis to draw conclusions about whether osteosarcoma incidence and fluoridation are causally linked. Furthermore, this study, while more detailed, is based on the small number of cases that occurred during the study years in the fluoridated areas of New Jersey. Because there is definite value in the decreased number of dental caries resulting from exposure to the beneficial level of fluoride, additional epidemiologic investigations should be conducted in order to pursue the issue of relative risks and benefits of fluoride ingestion from all sources.”

• Ecological studies of general populations

  o Cancer mortality study of 35 U.S. cities: Chilvers (1983)

    Cancer mortality and fluoridation of water supplies in 35 US cities.
    Chilvers C.

    Abstract: “The possibility of a cancer risk associated with fluoridation of public water supplies is re-examined using mortality data for 35 US cities, 20 with fluoridated water supplies and 15 with non-fluoridated water. Crude cancer death rates, and mortality ratios standardized for age, sex, and ethnic group are examined, using four alternative sets of standard rates and three different combinations of periscensal years’ deaths. Changes in cancer mortality before and after fluoridation in the fluoridated cities are compared with changes in the non-fluoridated cities over the same time period. In none of the analyses have differences in mortality trends been found that could not be due to chance alone. Thus, these results do not support the suggestion of an association between fluoridation of water supplies and cancer mortality.”
References from Office of Environmental Health Hazard Assessment. March 2009
Chemical for CIC Consultation: Fluoride and Its Salts
Comments and Abstracts: Howard Pollick, BDS, MPH

o Cancer mortality study in England: Chilvers and Conway (1985)
  Cancer mortality in England in relation to levels of naturally occurring fluoride in water supplies.
  Chilvers C, Conway D.
  J Epidemiol Community Health. 1985 Mar;39(1):44-7
  Abstract: "Sixty-seven small areas in England have been classified into four groups according to the level of naturally occurring fluoride in their water supplies. Small area mortality statistics for 1969-73 have been used to look for differences in cancer mortality in relation to fluoride levels. Deaths from all cancers and from cancer at 12 specific body sites have been examined; no consistent trends in mortality are apparent. These results provide no evidence of a harmful effect of naturally occurring fluoride in water supplies."

  International trends in the incidence of bone cancer are not related to drinking water fluoridation.
  Freni SC, Gaylor DW.
  Abstract: "BACKGROUND. Because osteosarcomas may develop in rats exposed to fluoridated water, water fluoridation might pose a cancer risk to humans. METHODS. A time trend analysis of the cumulative risk (CR) of bone cancer for the period 1958-1987 for 40 cancer registry areas showed an increased risk for young males in Canada, Europe, and the United States, and a decreased lifetime risk for either sex in Europe. RESULTS. This was unrelated to water fluoridation and may have resulted from changes in coding practices. Bone cancer risk was inversely related to the incidence of cancers of unknown origin, suggesting that bone metastases were erroneously coded as primary bone cancer. In 1968-1972, most areas recorded more bone cancer deaths than new cases of the disease. CONCLUSIONS. The mortality/incidence ratio, but not the incidence rate (IR), has dropped sharply since then, which erodes the basis of past inferences relating cancer mortality to fluoridation."

o Study of fluoridation and cancer mortality in individuals > 45 years of age in New Zealand: Goodall et al. (1980)
  Fluoridation and cancer mortality in New Zealand.
  Goodall CM, Foster FH, Fraser J.
  Abstract: "Claims that fluoridation of the municipal water supply causes cancer in humans have not been substantiated by independent objective studies in the United States of America, Canada, or New Zealand. After thorough reexamination of the earlier publications from other countries, and our own study of data available for the New Zealand population, we consider the 1976 statement of the Royal College of Physicians seems more than ever justified: "There is no evidence that fluoride increases the incidence or mortality of cancer in any organ"."

  Fluoridated drinking water and the occurrence of cancer.
  Hoover RN, McKay FW, Fraumeni JF Jr.
  Abstract: "A recent report by the National Health Federation, a private agency, related cancer mortality patterns in the United States to fluoridation of water supplies, triggering much public health concern and some political response. To clarify the issues raised, we studied cancer mortality and incidence statistics for U.S. counties, 1950-69. No trends could be ascribed to the consumption of water that is artificially or naturally fluoridated."

o Study of the relationship between drinking water fluoridation and osteosarcoma in Alberta, Canada: Hrudey et al. (1990)
  Drinking water fluoridation and osteosarcoma.
  Hrudey SE, Soskolne CL, Berkel J, Fincham S.
From the 2006 NRC report (page 322): “The Hrudey et al. (1990) osteosarcoma incidence study in Alberta, Canada, and the Freni and Gaylor (1992) mortality analysis of bone cancer for 40 cancer registries worldwide found no evidence of association with fluoride.” Page 336: “As pointed out by Hrudey et al. (1990), rare diseases such as osteosarcoma are difficult to detect with good statistical power.”

o Study of cancer incidence in relation to fluoride level in water supplies: Kinlen (1975)
Cancer incidence in relation to fluoride level in water supplies.

o Time-trend study of bone cancer incidence rates in New York State related to fluoridation of drinking water: Mahoney et al. (1991)
Bone cancer incidence rates in New York State: time trends and fluoridated drinking water.
Mahoney MC, Nasca PC, Burnett WS, Melius JM.
Abstract: “BACKGROUND: Recent animal studies of the potential carcinogenicity of fluoride prompted an examination of bone cancer incidence rates. METHODS: Trends in the incidence of primary bone cancers, including the incidence of osteosarcomas were examined among residents of New York State, exclusive of New York City. Average annual osteosarcoma incidence rates in fluoridated and non-fluoridated areas were also compared. RESULTS: Among persons less than 30 years of age at diagnosis, bone cancer incidence among males demonstrated a significant increase since 1955, while incidence among females has remained unchanged. A significant decrease in bone cancer incidence rates since 1955 was observed among both males and females age 30 years and over at time of diagnosis. Osteosarcoma incidence rates have remained essentially unchanged since 1970, among both younger and older males and females. The average annual age adjusted incidence of osteosarcomas (1976-1987) in areas served by fluoridated water supplies was not found to differ from osteosarcoma incidence rates in non-fluoridated areas. CONCLUSIONS: These data do not support an association between fluoride in drinking water and the occurrence of cancer of the bone.”

o Study of the relationship between the incidence of osteosarcomas in adult males and water fluoridation, using SEER data: Appendix F of DHHS (1991)
http://health.gov/environment/ReviewofFluoride/
http://health.gov/environment/ReviewofFluoride/MAJfind.htm#can
Quote: “The NCI also conducted a more detailed evaluation of osteosarcomas using nationwide age-adjusted incidence data from the entire SEER database for the years 1973-1987 (Appendix F). Osteosarcoma is a rare form of bone cancer, the cause of which is under study. Approximately 750 newly diagnosed cases occur each year in the United States, representing about 0.1 percent of all reported cancers. Between two time periods, 1973-1980 and 1981-1987, there was an unexplained increase in the annual incidence rates of osteosarcoma in young males under age 20 from 3.6 cases per 1,000,000 people (88 registry cases) to 5.5 cases per 1,000,000 people (95 registry cases). This compares to a decrease in young females of the same age group from 3.8 cases per 1,000,000 people (87 registry cases) to 3.7 cases per 1,000,000 people (63 registry cases). The amount of increase observed in young males was greater in fluoridated than in non-fluoridated areas. Although the reason for the increase in young males remains to be clarified, an extensive analysis reveals that it is unrelated to the introduction and duration of fluoridation. In studying rare cancers, such as osteosarcoma, small increases in risk, on the order of 5 to 10 percent, would not likely be detected. While descriptive epidemiological studies are useful in determining whether or not there is a credible association, the qualitative nature of any association, if one exists, can best be determined through more refined methods, such as case-control studies.”

o Study of osteosarcoma, seasonality and environmental factors in Wisconsin: Moss et al. (1995)
Moss ME, Kanarek MS, Anderson HA, Hanrahan LP, Remington PL.
Arch Environ Health. 1995 May-Jun;50(3):235-41
Abstract: "Proxy exposure measures and readily available data from the Wisconsin Cancer Reporting System were used to contrast 167 osteosarcoma cases with 989 frequency-matched cancer referents reported during 1979-1989. Differences in potential exposure to water-borne radiation and fluoridated drinking water, population size for the listed place of residence, and seasonality were assessed. An association was found between osteosarcoma and residence in a population of less than 9,000 (odds ratio = 1.6, 95% confidence interval = 1.1-2.4). In addition, an association between month of birth (May through July versus other months of birth) and osteosarcoma among individuals who were less than 25 y of age (odds ratio = 1.9, 95% confidence interval = 1.1-3.4). Overall, no association was found between potential exposure to fluoridated drinking water and osteosarcoma (odds ratio = 1.0, 95% confidence interval = 0.6-1.5). The association between osteosarcoma and water-borne radiation was weak and was not significant statistically (odds ratio = 1.5, 95% confidence interval = 0.8-2.8)."

Global study of cancer incidence rates and environmental factors including fluoridated drinking water: Steiner (2002)
Cancer incidence rates and environmental factors: an ecological study.
Steiner GG.
Abstract: "The environmental factors latitude, temperature, and water consumption have been correlated with cancer incidence rates. To date, there is no consensus of opinion that explains how these environmental factors alter the incidence of cancer. A fluoride belt stretches across the north and east of Africa, through the Middle East, across Pakistan and India, into Southeast Asia, and the south of China. There appears to be an association between areas with low cancer incidence rates and high fluoride concentrations in the water supply. This ecologic study attempts to determine if fluoride is correlated with cancer incidence rates. If so, this study also attempts to determine whether fluoride is a factor in the correlation between latitude, temperature, and cancer incidence rates. Population groups with very high cancer incidence rates and population groups with very low cancer incidence rates are compared to identify environmental factors that might explain the correlation between cancer incidence rates and the environmental factors of latitude, temperature, and fluoride. There is a positive correlation between cancer incidence rates and latitude (r = 0.71). There is an inverse correlation between cancer incidence rates and temperature (r = -0.87). There is also an inverse correlation between cancer incidence rates and fluoride concentration in the drinking water (r = -0.75). Very low cancer incidence was found in areas with high fluoride concentrations in the drinking water.”

Study of fluoridated drinking water and cancer mortality in Taiwan: Yang et al. (2000)
Fluoride in drinking water and cancer mortality in Taiwan.
Yang CY, Cheng MF, Tsai SS, Hung CF.
Environ Res. 2000 Mar;82(3):189-93.
Abstract: "The possibility that cancer risk is associated with naturally fluoridated water in Taiwan is examined. The 1982-1991 age-adjusted mortality rates for cancer for 10 municipalities whose water supplies contained the highest naturally occurring fluoride concentrations in Taiwan were compared to those rates for 10 matched municipalities with unfluoridated water. The two groups had similar urbanization levels and sociodemographic characteristics. Our study does not support the suggestion that fluoridation of water supplies is associated with an increase in cancer mortality in Taiwan.”

Study of the relationship between cancers at 36 tissue/organ sites and exposure to fluoridated drinking water in the U.S., using data from the International Agency for Research on Cancer: Takahashi et al. (2001)
Takahashi K, Akiniwa K, Narita K.
Abstract: "Age-specific and age-standardized rates (ASR) of registered cancers for nine communities in the U.S.A. (21.8 million inhabitants, mainly white) were obtained from IARC data (1978-82, 1983-87, 1988-92). The
percentage of people supplied with "optimally" fluoridated drinking water (FD) obtained from the Fluoridation Census 1985, U.S.A. were used for regression analysis of incidence rates of cancers at thirty six sites (ICD-WHO, 1957). About two-thirds of sites of the body (ICD) were associated positively with FD, but negative associations were noted for lip cancer, melanoma of the skin, and cancers of the prostate and thyroid gland. In digestive organs the stomach showed only limited and small intestine no significant link. However, cancers of the oral cavity and pharynx, colon and rectum, hepato-biliary and urinary organs were positively associated with FD. This was also the case for bone cancers in male, in line with results of rat experiments. Brain tumors and T-cell system Hodgkin's disease, Non-Hodgkin lymphoma, multiple myeloma, melanoma of the skin and monocytic leukaemia were also correlated with FD. Of the 36 sites, 23 were positively significant (63.9%), 9 not significant (25.0%) and 4 negatively significant (11.1%). This may indicate a complexity of mechanisms of action of fluoride in the body, especially in view of the coexisting positive and negative correlations with the fluoridation index. The likelihood of fluoride acting as a genetic cause of cancer requires consideration."

Animal carcinogenicity data

• Two-year drinking water animal bioassays
  o B6C3F1 mice: NTP (1990)
  o F344/N rats: NTP (1990)
National Toxicology Program (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, National Institutes of Health.
  
  http://ntp.niehs.nih.gov/?objectid=0709411C-E355-A12E-DBB666806CB8DB2

  Abstract for TR-393 - Sodium Fluoride
  TR-393 Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1, Mice (Drinking Water Studies)
  Quote: "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 drinking water for 2 years." (end quote)

• Long-term diet animal bioassays
  o 97-week studies in CD-1 mice: Maurer et al. (1993)
  
  Confounded carcinogenicity study of sodium fluoride in CD-1 mice.
  
  Abstract: "To determine its carcinogenic potential, sodium fluoride (NaF) was fed to CD-1 mice for up to 97 weeks. Mice given NaF at a dose of 4, 10, or 25 mg/kg of body weight per day added to a low-fluoride diet were compared to controls given either an unsupplemented low-fluoride diet or laboratory chow. Nonneoplastic changes consistent with those previously recognized from fluoride toxicity were observed in teeth, bones, and joints. Unexpectedly, osteomas occurred in all groups. The incidence of osteomas was similar in groups given the low-fluoride control diet, laboratory chow, or NaF doses of 4 or 10 mg/kg per day. The incidence of osteomas in these groups was increased over that historically experienced at the laboratory and reported in the literature for CD-1 mice. The incidence of osteomas in the mice given 25 mg NaF/kg per day added to a low-fluoride diet was increased over that in the other groups. Osteomas were first observed at Week 55. No malignant bone tumors were observed during the course of the study. The locations, multiplicity, and morphologic features of the osteomas in all groups were similar to those associated with virus-induced bone tumors. Electron microscopic examination revealed abundant retrovirus particles in all osteomas
examined from control and test mice. It was concluded that the study was confounded by a retrovirus which contributed to the induction of the osteomas. Because the study was confounded, it cannot be considered a valid bioassay to be used for risk assessment.

99-week studies in Sprague-Dawley rats: Maurer et al. (1990)
Maurer JK, Cheng MC, Boysen BG, Anderson RL.
Abstract: "To determine the carcinogenic potential of sodium fluoride (NaF), we fed Sprague-Dawley rats a diet containing NaF for up to 99 weeks. Rats receiving NaF at a dose of 4, 10, or 25 mg/kg per day added to a low-fluoride diet were compared with controls receiving either a low-fluoride diet or laboratory chow. Each treatment group consisted of 70 rats of each sex. A 30% decrement in weight gain occurred at an NaF dose of 25 mg/kg per day. Evidence of fluoride toxicity was seen in the teeth, bones, and stomach, and the incidence and severity of these changes were related to the dose of NaF and the duration of exposure. Despite clear evidence of toxicity, NaF did not alter the incidence of preneoplastic and neoplastic lesions at any site in rats of either sex. Results from this study indicate that NaF is not carcinogenic in Sprague-Dawley rats."

Other relevant data

• Genotoxicity evidence: recent reviews and some individual studies:
  Quote (page 132): “In general, positive genotoxicity findings occurred at doses that are highly toxic to cells and whole animals. Lower doses were generally negative for genotoxicity.”
  NRC (2006, Chapter 6)
  Quote (page 193): “Overall, the available studies of fluoride effects on human reproduction are few and have significant shortcomings in design and power, limiting inferences.”
  http://books.nap.edu/openbook.php?record_id=11571&page=204
  Quote (page 204): “A large number of reproductive and developmental studies in animals have been conducted and published since 1990, and the overall quality of the database has improved significantly. High-quality studies in laboratory animals over a range of fluoride concentrations (0-250 mg/L in drinking water) indicate that adverse reproductive and developmental outcomes occur only at very high concentrations. A few studies of human populations have suggested that fluoride might be associated with alterations in reproductive hormones, fertility, and Down’s syndrome, but their design limitations make them of little value for risk evaluation.”
  o Salmonella reverse mutation assay: Li et al. (1987)
  Absence of mutagenic and antimutagenic activities of fluoride in Ames salmonella assays.
  Li Y, Dunipace AJ, Stookey GK.
  Mutat Res. 1987 Apr;190(4):229-36.
  Abstract: “The mutagenicity of fluoride (as sodium fluoride, NaF) was investigated with Ames Salmonella/microsome assays in strains of TA97a, TA98, TA100, TA102 and TA1535. The concentrations of NaF tested ranged from 0.44 to 4421 micrograms/plate (0.1 to 1000 ppm F), both with and without microsome activation. In addition, the suggested antimutagenic effect of fluoride was evaluated with known mutagens at various concentrations of NaF (0.44-442.2 micrograms/plate, 0.1-100 ppm F). The data showed that NaF, in amounts from 0.44 to 442.2 micrograms/plate (0.1-100 ppm F), failed to significantly increase the number of
the revertants over the number observed in the solvent (distilled deionized water) controls. Increases of NaF to, and beyond, 1100 micrograms/plate (250 ppm F) resulted in a toxic effect and a reduction of the revertants to various degrees among the strains. NaF in the presence of known mutagens did not significantly decrease the number of the revertants. The results of this study indicate that NaF does not have mutagenic or antimutagenic effects in the strains tested with Ames Salmonella assays.”

Mouse lymphoma cell thymidine kinase locus mutation assay: Caspary et al. (1987 and 1988)  
Human lymphoblast TK6 cells: Caspary et al. (1988)

**Mutagenic activity of fluorides in mouse lymphoma cells.**
Abstract: “The L5178Y mouse lymphoma cell forward-mutation assay was used to test for the mutagenic activity of sodium and potassium fluoride at the thymidine kinase locus. Mutants were detected by colony formation in soft agar in the presence of trifluorothymidine. Mutagenic and toxic responses were observed in the concentration range of 300-600 micrograms/ml with both sodium and potassium fluoride. Approximately 3-fold increases in mutant frequency were observed for concentrations in the 500-700 micrograms/ml range that reduced the relative total growth to approximately 10% in the absence or presence of a rat-liver S9 activation system. A sample of 30% sodium fluoride-70% sodium bifluoride (NaHF2) induced a similar mutagenic response but was more toxic with respect to the fluoride concentration. A specificity for fluoride ions in causing mutagenesis was indicated by the fast (sic) that much higher concentrations of sodium or potassium chloride were necessary to cause toxicity and increases in the mutant frequency. The possible involvement of chromosomal changes was signaled by the predominant increase in the small colony class of mutants.”

**The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells.**
Abstract: “The mutagenic (TFT resistance) and toxic responses of mouse lymphoma (MOLY) L5178Y cells and human lymphoblast (HULY) TK6 cells were compared for 13 chemicals. The mutagenic activities of 8 of the 13 chemicals (62%) examined in the HULY and MOLY assays are in agreement - the results being judged positive in both assays. However, a dramatic difference is observed when the two conditions of metabolic activation are considered separately; the overall concordance of 8/13 has been achieved by combining a 13/13 (100%) agreement in the absence of S9 with a 1/6 (17%) agreement in the presence of S9. In the absence of S9, the concentration ranges, lowest significant doses, and shapes of the concentration-response curves for both toxicity and mutagenicity were similar in spite of the differences in exposure times (4 h for MOLY, 20 h for HULY) and expression times (2 days for MOLY, 3 days for HULY). The general agreement observed in the absence of S9 contrasted with the differences manifested in its presence. 6 compounds which were negative in the absence of S9 were tested in both the MOLY and HULY assays in the presence of S9. Of the 6 chemicals, only 1 was positive in both MOLY and HULY under the latter condition; 4 others were positive in MOLY and negative in HULY whereas 1 was positive in HULY and negative in MOLY.”

**Reviews**

(Page 1) Public Health Statement.
Quote: “This public health statement tells you about fluorides, hydrogen fluoride, and fluorine and the effects of exposure presented in the toxicological profile. These profiles were specifically prepared by ATSDR for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List (Superfund sites) and are intended to describe the effects of exposure from chemicals at these sites.” (end quote)

“The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Fluorides, hydrogen fluoride, and fluorine have been found in at least 188 of the 1,636 current or former NPL sites.”

(Page 18):
“Numerous community-based studies have examined the possible association between fluoridated water and cancer. Most of these studies did not find significant associations between water fluoridation and cancer mortality or site-specific cancer incidence. Some studies have found associations between water fluoridation and cancer mortality/incidence or site-specific cancer incidence (osteosarcoma or bone cancer). The lack of control for potential confounding variables (i.e., age, race) limits the interpretation of the total cancer study results. The weight of the evidence indicates that fluoridation of water does not increase the risk of developing cancer. A 2-year study in rats found a weak, equivocal fluoride-related increase in the occurrence of osteosarcomas in male rats, and no evidence of carcinogenicity in female rats or male or female mice. IARC has determined that the carcinogenicity of fluoride to humans is not classifiable.”

• National Research Council: NRC (2006)

Page 9-10: “On the basis of the committee’s collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells in vitro), the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed. Assessing whether fluoride constitutes a risk factor for osteosarcoma is complicated by the rarity of the disease and the difficulty of characterizing biologic dose because of the ubiquity of population exposure to fluoride and the difficulty of acquiring bone samples in nonaffected individuals.

Page 11: “The committee’s conclusions regarding the potential for adverse effects from fluoride at 2 to 4 mg/L in drinking water do not address the lower exposures commonly experienced by most U.S. citizens. Fluoridation is widely practiced in the United States to protect against the development of dental caries; fluoride is added to public water supplies at 0.7 to 1.2 mg/L. The charge to the committee did not include an examination of the benefits and risks that might occur at these lower concentrations of fluoride in drinking water.”

Page 16: “Water fluoridation is supported by the Centers for Disease Control and Prevention (CDC) as one of the 10 great public health achievements in the United States, because of its role in reducing tooth decay in children and tooth loss in adults (CDC 1999). Each U.S. Surgeon General has endorsed water fluoridation over the decades it has been practiced, emphasizing that “[a] significant advantage of water fluoridation is that all residents of a community can enjoy its protective benefit . . . A person’s income level or ability to receive dental care is not a barrier to receiving fluoridation’s health benefits”.”

Page 316: “Update on Genotoxicity: Conclusions and Recommendations of NRC (1993). Overall, the results in in vitro systems summarized above are inconsistent and do not strongly indicate the presence or absence of genotoxic potential for fluoride. In 1993, NRC concluded that the existing genotoxicity data probably were not of “genetic significance.” There were no specific 1993 NRC recommendations regarding genotoxicity studies, although the report did mention the dearth of human in vivo assays. The more recent literature on in vitro assays does not resolve the overall inconsistencies in the earlier literature. The human population in vivo studies published during the past 10 years comprise a new body of data that might be pertinent to evaluating...
the genotoxic potential of fluoride; those population studies by definition integrate the pharmacokinetic contexts and actual cell environment parameters resulting from external exposures, whether via water or other environmental media. However, the inconsistencies in the results of these in vivo studies do not enable a straightforward evaluation of fluoride’s practical genotoxic potential in humans.”