

# Evidence supporting prioritizing fluoride for carcinogenicity hazard identification

by

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Fluoride and its salts (abbreviated “F” hereafter) are being assessed for priority in conducting a Hazard Identification by your committee. The most recent and authoritative review of the toxicology and potential carcinogenicity of F was conducted by the US National Research Council (NRC) and published in 2006.

The NRC 2006 review concluded:

Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed (Tables 10-4 and 10-5). As noted above, osteosarcoma is of particular concern as a potential effect of fluoride because of (1) fluoride deposition in bone, (2) the mitogenic effect of fluoride on bone cells, (3) animal results described above, and (4) pre-1993 publication of some positive, as well as negative, epidemiologic reports on associations of fluoride exposure with osteosarcoma risk. [NRC 2006, p 286]

The strongest positive epidemiological study to date, a case-control study by Bassin et al 2006, was not considered in this review because it was not published until several months after the NRC review was finalized. Most of the questions the NRC had about an early unpublished version of Bassin’s work were answered in her 2006 paper, further shifting the weight of evidence toward a conclusion that F is a carcinogen.

A letter to the editor from Douglass raised unspecified cautions about Bassin’s results [Douglass 2006]. The only reason offered for questioning Bassin’s results was because they differed from preliminary results in Douglass’ own Phase 2 study. But Douglass gave insufficient details to assess the comparability or validity of his study. Douglass has a long history of issuing preliminary announcements about his F-osteosarcoma studies, all of which claim no association has been found [McGuire 1995, Douglass 1998, Douglass 2002, Douglass 2004]. Funding for his study began in 1992 and today,

17 years later, he has yet to publish a single paper on F and osteosarcoma. It is also important to understand that the data Bassin used in her analyses was gathered by Douglass during a Phase 1 of his study. In a conference abstract in 1995 Douglass had claimed that his “preliminary” analysis of this same Phase 1 data found no association between F and osteosarcoma [McGuire 1995]. So, Douglass’ preliminary analyses have not been born out in later full analyses by others, using the same data

Reference is often made to the 2000 York Review for the UK [NHS Centre for Reviews 2000]. This review is weaker than the NRC’s because it excluded all animal and *in vitro* evidence and predated several important positive studies. A recent Australian government review essentially summarized the findings of the York Review and added a cursory discussion of more recent evidence [Yueng 2008]. Prominent attention is paid to Douglass’ letter to the editor, with the implication that this unsubstantiated letter counterbalances the weight of Bassin’s peer-reviewed paper.

It is worth noting that both the York Review and the Australian review were commissioned by government agencies which strongly promote fluoridation. In contrast, the NRC Review was commissioned by the US EPA, which does not have any official policy of promoting fluoridation.

## Comments on OEHHA screening results

Results of OEHHA’s initial evidence screening summary for F are shown below. We provide some details on the strength of the identified evidence, along with additional evidence that may have been missed by the screens. The **X**’s in black mark OEHHA’s screening conclusions. Below those, we have added a line of red **X**’s to indicate where we believe additional evidence exists. Details are provided below.

Exposure				Human Data				Animal Data				Other Relevant Data					
Widespread	High in frequent consumers	Limited / occupational	High in infrequent consumers	Analytical	Descriptive	Case series / reports	Analytical: mixed / poorly defined exposures	Two or more studies	One study w/ unusual incidence, site/type, age at onset	One study and second study with benign tumors only	One study	Tumor initiation / promotion or co-carcinogenicity studies	Genotoxicity	Carcinogenic metabolites	Structural similarity with tumorigens or P65 carcinogens	Hormonal activity / disruption	Other mechanistic studies
X				X					X				X				
X	X			X	X				X	X			X			X	X

From:

[http://www.oeaha.ca.gov/prop65/CRNR\\_notices/state\\_listing/prioritization\\_notices/pdf/Chemicals030509.pdf - page=5](http://www.oeaha.ca.gov/prop65/CRNR_notices/state_listing/prioritization_notices/pdf/Chemicals030509.pdf - page=5)

## Exposure screen

### Very widespread and unavoidable exposure

Human exposure to fluoride is probably more widespread and unavoidable than any of the other 38 proposed substances. In the USA 60% of the population has drinking water where F has been added with the intention of reducing dental decay. In CA, 27% of residents on public water systems in 2006 drank fluoridated water, and with recent state fluoridation decisions, the level is expected to increase substantially [CDC 2009]. But even people whose home tap water is not fluoridated can not easily avoid fluoride, because any beverages or processed foods they consume in fluoridated areas or that originate in fluoridated areas will contain fluoride. Most of the major metropolitan areas of CA including Los Angeles and San Francisco/Oakland are fluoridated. Many beverage bottling and food processing plants use fluoridated municipal water so the F becomes incorporated into their products [USDA 2005]. Unlike most other proposed chemicals which are unintended contaminants from industrial pollution or pesticide residues, fluoride is purposely added to drinking water and makes its way through foods and beverages into virtually all consumers. It is very difficult to avoid exposure.

Infants fed formula reconstituted with fluoridated water at 1 mg/L will receive approximately 250 times more fluoride than a breast fed infant. [NRC, 2006, p.33 and Table 2-6, p.40]

Additional exposures occur through dental products, many of which contain very high levels of F. For example, over 95% of the toothpaste sold is fluoridated with F levels of 1000-1500 mg/kg. Both children and adults typically swallow some of their toothpaste, even if not intentionally.

Two registered pesticides, cryolite and sulfuryl fluoride, yield F residues in agricultural products and processed foods. The F tolerances in common foods such as wheat flour and "all processed foods" are 70 mg/kg [EPA 2005, EPA 2004, FAN 2005]. Sulfuryl fluoride is a recently approved fumigant on foods so it is not clear how much additional F exposure it will produce in the general population and amongst specific groups consuming foods high in F residues.

Tea and iced tea from powder both contain elevated F levels, estimated by USDA to be about 3 times more than fluoridated water [USDA 2005b]. Tea drinkers may receive substantial F exposure even if they do not have fluoridated tap water.

The most direct exposure assessment for F comes from surveys of childhood dental fluorosis, a biomarker for fluoride exposure [Brunelle 1987]. Large-scale national surveys have found that even children growing up with unfluoridated water have a 22% rate of fluorosis and as many as 48% with fluoridated water exhibit this overexposure [Heller 1997, Beltran 2007]. Dental fluorosis occurs when exposure is more than

approximately 0.05 mg/kg-bodyweight/day during childhood. In surveys conducted before widespread fluoridation of water began, only about 1% of children in uncontaminated areas had dental fluorosis, so there is a 20-fold increase in high exposure cases even amongst those today who do not have fluoridated tap water.

### **“Frequent consumers” constitute a large portion of the population**

The exposure screen should also be modified to indicate that “frequent consumers” will get especially high F exposures. For F, the description “frequent consumer” would apply to anyone who drinks more water than average. There is a very wide range of water consumption per bodyweight with top consumers drinking many times more water than the average. All exposure assessments except NRC 2006 have considered only average water consumption, so they have seriously underestimated exposure in the group of “frequent consumers”.

As mentioned, tea has naturally high F, so the large number of tea drinkers should also be classified as “frequent consumers”.

### **Human metabolism and tissue-specific exposure**

Although there is no exposure screening criteria that addresses internal tissue exposure levels, it is relevant to point out that F is unusual in the extent that it partitions internally into skeletal tissues. F is a strongly “bone-seeking” chemical. The bone tissue level of F is typically tens of thousands of times higher than the serum and soft tissue levels. F has a biological half-life in bones estimated as long as 20 years, so bone F concentration rises steadily with age [NRC 2006, p 92]. About 50% of ingested F will be retained in the body, with most concentrated in the skeleton. The remainder is excreted by the kidneys. But for those with impaired kidney function due to disease or simply age over 50, F excretion is reduced so bone levels reach even higher levels.

## **Human data screen**

### **Analytical study evidence**

The leading analytical study providing positive evidence of carcinogenicity is Bassin 2006. This was a careful case-control study with a relatively large sample size and controlling for a number of potential confounders. The adjusted odds ratio (OR) for osteosarcoma in young males for exposure during the most susceptible time window was 5.46 (95% CI 1.50, 19.90).

The only other relatively large published case-control study of osteosarcoma [Gelberg 1995] had several potentially serious problems which may have led to underestimation of the risk of osteosarcoma from drinking water F. The authors concluded that the observed elevated risks were not large enough or consistent enough to be considered

evidence for a positive association between F and osteosarcoma. However, the NRC 2006 review was not as dismissive of the evidence.

We have examined Gelberg's study closely and have recently been able to confirm that she failed to control for age in any of her analyses. Since she used age matching, and because fluoride exposure strongly correlates with age, her unadjusted results will suffer from a form of selection bias. The bias will be toward the null, or no association. A full description of why failure to control for a matching variable can result in bias toward the null can be found in Rothman & Greenland's *Modern Epidemiology, 2<sup>nd</sup> Edition* [Rothman 1998, p 151]. So, the suggestive evidence of carcinogenicity that NRC 2006 noted in the Gelberg study is likely to be stronger when the necessary age adjustment is applied. It should be noted that Bassin did report adjusting for age in all her analyses.

A very recently published case-control study lends evidence that F exposure may cause osteosarcoma and other types of bone cancers. Sandhu 2009 compared serum F levels in two sets of cases and one control group recruited at a hospital in India. The groups were: 25 osteosarcoma cases; and an age and sex matched group of 25 non-osteosarcoma bone cancer cases; and a control group of 25 patients being seen for musculo-skeletal pain but with no cancer. The province in India where the study was conducted has regions with high natural F in drinking water. The average serum F level of osteosarcoma cases was twice as high as the bone cancer cases, and 3.5 times higher than in the controls. All differences were statistically significant.

The OEHHA screening document notes that F has "analytical" study evidence for carcinogenicity, but fails to note that there are also several ecological and semi-ecological "descriptive" studies which provide evidence of human carcinogenicity. The strongest semi-ecological study (using both individual level data and group level data) is Cohn's 1992 study for the New Jersey Department of Health. It used individual data on age, sex, race, and town of residence for osteosarcoma cases from the NJ Cancer Registry. Exposure was estimated from the F level in the drinking water of the town at the time of diagnosis. This is a more accurate estimate than was used in all other ecological studies of F which relied on average F levels in entire counties or even states/provinces. Despite relatively small numbers of cases, the effect size was large with a rate ratio as high as 8.0 (95%CI 3.9-15) amongst young white males in one analysis. A number of likely confounders were controlled.

The other commonly cited ecological study of fluoride and bone cancer was by Hoover 1991. Hoover did two analyses, the first compared changes in bone cancer rates in counties after fluoridation with rates in nearby unfluoridated counties. This analysis found an almost 100% increase in rates in young males in fluoridated counties compared to unfluoridated. Hoover then conducted additional analyses which failed to confirm the first analyses. However, the additional analyses had weaknesses and errors which invalidates them, leaving his original positive findings standing.

The weaknesses occurred because stratification into numerous categories led to very small numbers in each category and unstable rates. To try to increase numbers Hoover loosened inclusion criteria to the point that counties were no longer being compared to nearby counties, but to counties in distant states.

A serious error arose because the majority of the counties Hoover classified as “non-fluoridated”, in fact had enough natural F in drinking water that they should have been classified “fluoridated” or excluded from the analysis. His first analysis was unaffected by natural F because it only looked at changes in osteosarcoma rates following artificial fluoridation. But his additional analyses were essentially geographical comparisons between different sets of counties. For these, natural F could not be ignored.

Several small case-control studies of osteosarcoma and F were conducted in the early 1990s, but all suffered from weaknesses which limit their informativeness. We have discussed these in more detail in an accompanying document.

Similarly, our accompanying document discusses a number of ecological studies conducted in the 1990s, which also are relatively uninformative due to various limitations.

A newer ecological study looking at rates of osteosarcoma in provinces of Kenya should also be considered [Neurath 2005]. The measure of F exposure in this study was average rate of dental fluorosis by province. Dental fluorosis is a reliable biomarker of childhood F overexposure from all sources of F, not just drinking water. Osteosarcoma rates by province came from a national tumor registry maintained by Kenya’s main central hospitals. Linear regression showed a strong correlation between rate of dental fluorosis and rate of osteosarcoma incidence. Age and sex distribution data was unavailable.

Additional human analytical evidence exists from occupational cohort studies. In a very long running series of studies looking at mortality amongst workers at a cryolite factory in Denmark, Grandjean found evidence that F may be a risk factor for both bladder and lung cancer [Grandjean 2004, Grandjean 1992, Grandjean 1982]. The cohort was followed for more than 50 years until almost all had died. Their workplace exposures to cryolite dust resulted in well-documented high F exposures, but no other exposures to any known carcinogens. No information was available on smoking history, but the pattern of mortality suggested that smoking was no more common amongst the worker cohort than amongst the reference population of all Copenhagen residents. Deaths from respiratory disease were no more common in workers than the residents, suggesting that smoking probably did not account for the increases in lung and bladder cancer seen. Both tissues are sites where the F exposure would have been relatively high, since exposure was largely by inhalation and F is concentrated in the urine during excretion. Bone cancer was considered too rare for increases to have been detected in this cohort study.

Grandjean also reviews occupational cancer studies on aluminum workers who often receive high F exposure. A number of aluminum worker cohort studies have found increased risk of lung and bladder cancers, but rarely have the studies been able to distinguish risks from F compared to other chemicals common in the aluminum industry. Nevertheless, Grandjean considered it possible that the F could have played a role in the aluminum worker cancers.

## **Animal data screen**

The main animal study showing evidence of carcinogenicity was the National Toxicology Program (NTP) 1990 study in male rats [Bucher 1990]. Although only one sex seemed to be affected, there are biologically plausible mechanisms for this gender-specific effect, and human epidemiological studies have shown the same result.

F reaches tissue concentrations in the skeleton that are tens of thousands of times higher than in serum or soft tissues. So, the finding of an association between osteosarcoma and F fits closely with both plausible biological mechanisms and tissue-specific exposures. Osteosarcoma is a very rare tumor, especially in the animal models used.

Another significant point is that the exposure levels which appeared to cause osteosarcomas in the rat bioassay were, in comparison to most chemical cancer bioassays, very close to the actual human exposure levels. Measured as concentration in drinking water, there was an increased rate of osteosarcoma found in the exposure group which received only 45 mg/L F in drinking water. 1 mg/L is the standard level of F in fluoridated public drinking water. But humans are also less efficient at excreting and sequestering F than rats. Drinking the same concentration of F, humans will reach serum F levels 5-20 times higher than rats. On a tissue-specific exposure basis, even the highest dose rats in the NTP study had bone F levels that are reached by some people.

The only agents known to cause osteosarcoma in any mammalian species are high-energy ionizing radiation, especially from internal bone-seeking radionuclides, and chemical alkylating agents.

Most of the work on osteosarcoma and internal radionuclides has been on dogs, which are considered a more suitable model for osteosarcoma than rodents. Domestic dogs, especially larger breeds, get osteosarcoma at rates considerably higher than humans. To our knowledge, no experimental study of F and bone cancer in dogs has ever been published. Thus, the relative lack of animal evidence may be due to the fact that the most appropriate studies have not yet been done.

The OEHHA screen seems to have missed the existence of a second animal study which found clear evidence that F caused benign bone tumors, but not malignant bone tumors. This was the Maurer/Procter & Gamble 1993 study in mice where large

numbers of osteomas were found in a dose dependent relationship to F exposure. Osteomas are considered non-malignant tumors.

## **Other relevant data screen (genotoxicity etc.)**

The NRC 2006 review found evidence that fluoride disrupts hormone function so the screening category “hormonal activity/disruption” should be considered positive. Here is the NRC’s conclusion:

In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. Fluoride is therefore an endocrine disruptor in the broad sense of altering normal endocrine function or response, although probably not in the sense of mimicking a normal hormone. [NRC 2006, p223]

Fluoride is also well known as a potent disruptor of enzyme activity in many enzyme systems, some of which may affect hormones [Adamek 2005].

In addition, fluoride ion in the presence of the aluminum ion ( $\text{Al}^{3+}$ ) forms a complex  $\text{AlF}_4^-$  which is about the same size and shape as the phosphate ion. This aluminum fluoride complex is able to switch on G-proteins (see review Li, 2003) thus interfering with the trans-membrane messaging systems of water-soluble hormones and growth factors. In fact aluminum fluoride has been used in countless biochemical experiments to mimic the effect of certain hormones and deliver the signals without the hormone being present. Caverzasio has suggested fluoride stimulates bone growth (i.e. acts as an anabolic factor via  $\text{AlF}_4^-$  switching on G-protein normally activated by a growth factor.) [Caverzasio 1998].

The stimulation of bone growth; concentration in the bone and possible mutagenic activity of F all contribute to F being a highly plausible carcinogenic agent for bone.

The evidence that F is a hormone disruptor combined with the sex-specific risks of osteosarcoma from F in animal and human studies suggest that fluoride’s carcinogenic potential may occur through its affects on hormones. Bone growth and turnover is partially controlled by endocrine activity, so effects of F on the controlling endocrine systems may increase the risk of bone cancer.

The NRC 2006 review and most other recent reviews have concluded that there is sufficient evidence to judge F genotoxic. Details of the genotoxicity evidence are provided in an accompanying document.

A recent study found F effects in osteoblast cells on cell proliferation and apoptosis [Yan 2009].

A very recent paper confirms the genotoxic potential of F, but was additionally able to show genotoxicity at much lower levels than previous studies. Zhang 2009 used a new method to test genotoxicity in 20 known genotoxic agents including F, as well as 4 chemically similar but known non-genotoxic agents. All known agents including F tested positive and all known non-genotoxic tested negative. The detection level for F genotoxicity was as low as 0.5 mg/L. This level is far exceeded in bone tissues and can be reached even in serum after large exposures to F.

The NRC 2006 made estimates of intracellular fluid F concentration in the vicinity of osteoblast and osteoclast cells in bones. These are the cells thought to be involved in initiation of human osteosarcoma. The NRC estimated that the F concentration in these cells could reach over 1000 mg/L for osteoclasts and over 100 mg/L for osteoblasts. These concentrations are well above levels found to be genotoxic in *in vitro* studies. They are also above the levels (20-200 mg/L) typically used in experiments where aluminum fluoride switches on G-proteins.

## Summary

Based on the evidence described, we believe fluoride and its salts qualify for highest priority to conduct a Hazard Identification by OEHHA and CIC, as the next step toward possible listing as a carcinogen.

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