ENVIRONMENTAL WORKING GROUP

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Dr. C. W. Jameson
National Toxicology Program, Report on Carcinogens
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MD-EC-14
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Dear Dr. Jameson:

We are writing to nominate fluoride in tap water for inclusion in the Report on Carcinogens based on its ability to cause osteosarcoma in males less than 20 years of age.

The science supporting the link between fluoride and bone cancer in boys is compelling, and much of this science is recent and not reflected in current drinking water contaminant limits or the overall risk-benefit equation underlying the decision to add fluoride to the tap water of 170 million people. This widespread exposure to fluoride in tap water ensures that millions of boys are exposed during critical periods of development and growth that are relevant to the cancer in question.

EWG is aware of the value of fluoride to dentistry, yet a substantial and growing body of peer-reviewed science strongly suggests that adding fluoride to tap water may not be the safest way to achieve the dental health benefits of fluoridation. Based on a number of serious health concerns with fluoride, in 2002, the EPA commissioned a general review of the toxicity of fluoride by the National Research Council (NRC) of the National Academy of Sciences (NAS). Although the NRC panel will consider cancer effects in its comprehensive review, the committee is not charged with making a basic determination of fluoride's ability to cause bone cancer in boys. The NRC panel is comprised of individuals from a wide range of disciplines including dentistry, reproductive toxicology, neuroscience, biophysics, and epidemiology. Consequently it does not have the depth of expertise in carcinogenicity, the resources, or the mandate that the National Toxicology Program can bring to bear on this specific question. Only the NTP is in a position to undertake a thorough review of the total weight of the evidence supporting fluoride carcinogenicity – from the mechanistic data, through genotoxicity, animal cancer bioassays, and human epidemiologic studies.

## Summary of the science

The overall weight of the evidence strongly supports the conclusion that exposure to fluoride in tap water during the mid-childhood growth spurt between ages 5 and 10 increases the incidence of osteosarcoma in boys ages 10 through 19.

Biologically, the link between fluoride in tap water and bone cancer in boys is highly plausible. Fifty percent of ingested fluoride is deposited in bones, and fluoride is a mitogen that stimulates bone growth in the growing ends of the bones where the osteosarcoma occurs. Fluoride is also a confirmed mutagenic agent in humans, which suggests that fluoride can cause genetic damage in bone cells where it is actively deposited, in this case precisely where the osteosarcoma arises. Animal studies add further credence to the potential link between fluoride and bone cancer in males. The only two animal cancer bioassays conducted with fluoride both show rare bone tumors, many of which were malignant, in male as opposed to female test animals. And finally, three high quality epidemiology studies each show a strong association between fluoride in tap water and osteosarcoma in boys. While several epidemiology studies have failed to find an association between fluoride and osteosarcoma in boys, these studies typically did not look for a relationship between age of exposure to fluoride and the incidence of bone cancer in young males.

Osteosarcoma accounts for about 3 percent of all childhood cancers. The five-year mortality rate is around 50 percent, and nearly all survivors have limbs amputated, usually legs.

**Early concerns about cancer**

Concern about the ability of fluoride to cause bone cancer arose first in a 1977 NAS review of fluoride safety, where the academy committee expressed concerns about a high (13.5 percent) incidence in bone structure defects in the population of one of the nation's first fluoridated communities, Newburgh, New York compared to a 7 percent rate in the non-fluoridated Kingston community. At that time, the NAS recommended a full study of fluoride's potential to cause osteosarcoma in young boys. The resulting U.S. Public Health Service (USPHS) study was completed in 1991 and found a significant association between fluoride exposure and bone cancer in boys.

The 1991 USPHS study was based on data collected by the National Cancer Institute from 1973 through 1987. The first phase compared osteosarcoma rates in males under 20 years of age in fluoridated communities, with non-fluoridated communities in Iowa and around Seattle. The researchers found a 79 percent increase in osteosarcoma from 1973 through 1987 in fluoridated communities, compared to a 4 percent decrease over the same time period in non-fluoridated communities. A second phase of the study expanded the analysis nationwide, and found that the rates of osteosarcoma were 57 percent higher in the fluoridated communities than in communities with non-fluoridated water supplies (Hoover 1991).

As a follow-up to the USPHS study, the New Jersey Department of Health (NJDH) commissioned a similar study at the municipal level based on an individual's residence at the time of osteosarcoma diagnosis. The NJDH found that young males living in fluoridated communities had significantly higher rates of osteosarcoma than young males living in non-fluoridated areas; males 10-19 years old in fluoridated areas were 6.9 times more likely to develop osteosarcoma than those in non-fluoridated areas. According to the study authors, the findings "support the importance of investigating the possible link between osteosarcoma and overall ingestion of fluoride" (Cohn 1992).

Some experts questioned the significance of the NTP study findings when it was published citing the lack of an association between osteosarcoma and the length of time that individuals were exposed to fluoride in tap water. The overall weight of the scientific evidence, however, including a doctoral thesis from Harvard discussed below that closely examined timing of exposure in relationship to osteosarcoma incidence, provides compelling evidence that fluoride exposure during distinct mid-childhood periods of rapid bone growth is a much better indicator of osteosarcoma risk, than total duration, or average lifetime exposure.

Of the studies that have failed to find an association between fluoride in tap water and bone cancer (Operskalski 1987; McGuire 1991; Freni and Gaylor 1992; Moss 1995; Gelberg 1995), most have basic methodological issues that readily explain the negative findings. For instance, four of the five studies referenced above failed to analyze for age-specific effects, making it impossible for them to find such an association. The other (Operskalski) used friends and neighbors as controls, which according to one expert, Dr. Elise Bassin, produced a phenomenon called overmatching, where "detecting a benefit or risk for fluoride would be unlikely" (Bassin 2001, pg 78). Overall, as summarized by Bassin, "Prior studies have primarily evaluated fluoride exposure at the time of diagnosis or as an average lifetime exposure, and have not evaluated exposures at specific ages during growth and development when cell division is occurring rapidly" (Bassin 2001, pg 69).

**New Harvard doctoral thesis supports fluoride-bone cancer link**

Environmental Working Group (EWG) has attached to this petition, key portions of a doctoral dissertation from the Harvard School of Dental Medicine that found a strong, statistically significant relationship between fluoride in tap water at levels commonly found in American water supplies, and the rare but often fatal form of bone cancer, osteosarcoma, in boys. The association is particularly strong when exposure occurs during periods of rapid bone growth that take place between ages five and ten. The findings confirm the results of earlier studies by the U.S. Public Health Service and the New Jersey Department of Health that found an association between fluoride in tap water and bone cancer in males under age 20.

The dissertation by Elise Bassin is titled "Association between fluoride in drinking water during growth and development and the incidence of osteosarcoma for children and adolescents". Bassin was awarded a doctorate by the Harvard School of Dental Medicine in 2001. The research findings from her doctoral dissertation, however, have not yet been published.

The study came to the attention of EWG as a result of a failed attempt to obtain the full doctoral thesis by the staff of the National Research Council committee on fluoride safety. After being repeatedly denied a copy of the thesis, the NRC committee instead sent a committee member to the Harvard Countway Library of Medicine to read the entire document and report back to the committee. Environmental Working Group obtained a copy of the results section of the document from the Fluoride Action Network, who sent two researchers to the library, each of whom were allowed to copy 10 percent of the document.

Dr. Bassin's study measured the risk of osteosarcoma before age 20 based on exposures to fluoride in drinking water during each year of age in childhood. The methodology employed is rigorous and fluoride levels in tap water for each study participant were confirmed for each year of exposure during childhood. The analysis shows significantly elevated risks of bone cancer in boys exposed to fluoridated water during a window of vulnerability, from ages five through ten, with a peak risk associated with exposures at seven years of age.

Elevated bone cancer risks were identified by Bassin at fluoride levels that are commonly found in American water supplies. For drinking water systems with fluoride levels from 30 to 99 percent of the amount recommended by the Centers for Disease Control and Prevention (CDC), Bassin reports elevated risks for exposure from ages five through ten, with a five-fold risk of osteosarcoma for those exposed at age seven (4.94 (1.23-19.8) at 95% CI)). At 100 percent or more of the recommended level (and still far below legal maximum levels), the risk for exposure at seven years old rises to 7.2-fold (1.73-30.0) at the 95% CI (Bassin 2001, pg 95 – see results section attached).

The CDC's recommended fluoride levels are well below what is legally allowed in tap water. The EPA's maximum contaminant limit, or MCL, for fluoride in tap water is 4 parts per million. The CDC recommends optimal fluoride levels ranging from 0.7-1.2 parts per million based on average annual air temperatures and corresponding water consumption rates.

Notably, Bassin's doctoral dissertation was based on a reanalysis of data from another study that found no association between drinking water fluoride levels and bone cancer, co-authored by Harvard Department Chair Dr. Chester Douglass (McGuire 1995). In her reanalysis, Bassin examined the same cases and controls used by Douglass in 1995. Dr. Bassin, however, refined the analysis by limiting cases to individuals exposed at less than 20 years old and conducted a more detailed analysis of fluoride exposure and age-specific effects. The result was a very strong correlation between fluoride exposure and bone cancer, particularly for boys exposed at ages 6 through 8.

**Fluoride/cancer link in epidemiology studies is strongly supported by additional data**

When the results of USPHS, New Jersey, and Harvard (Bassin) studies are combined with the results of animal tests, human genotoxicity studies, and the known biochemistry and metabolism of fluoride, the overall weight of the evidence strongly supports a conclusion that fluoride causes the rare and often fatal bone cancer osteosarcoma in boys. Beyond human epidemiologic studies, the core supporting evidence includes the following:

- The two animal cancer bioassays conducted to date each found an increase in extremely rare bone tumors among male test animals in two species, rats and mice, exposed to fluoride (Maurer 1990; Maurer et al 1993; NTP 1990).

- Six separate studies have found that fluoride causes genetic mutations in humans (Meng 1995, 1997; Lazutka 1999; Sheth 1994; Wu 1995; Joseph 2000);

additional studies show that humans appear to be more sensitive to the genotoxicity of fluoride than rodents (Kishi 1993).

- The link between fluoride and osteosarcoma during periods of rapid growth is biologically highly plausible. Fluoride is a proven mitogen, meaning that it increases the proliferation of osteoblasts (bone formation) during periods of rapid skeletal growth (Gruber 1991; Kleerekoper 1996; Whitford 1996). As put by Dr. Bassin in her doctoral thesis: "It is biologically plausible that fluoride increases the rate of osteosarcoma, and that this effect would be strongest during periods of rapid growth, particularly in males" (Bassin 2001, pg 79).

- Over ninety percent of fluoride in the human body is stored in the bones; 50 percent of fluoride ingested is deposited directly into bones or teeth.

*Animal studies found bone cancer in male test animals*

Only two long-term animal cancer bioassays with fluoride have ever been conducted; one by the National Toxicology Program (NTP), and another by Procter and Gamble, which involved both rats and mice. Both found an increase in rare bone tumors among male animals exposed to fluoride.

In the NTP study, a dose-dependent increase of osteosarcoma was seen in the bones of fluoride-treated male rats (NTP 1990). These findings are highly significant for a number of reasons:

- Osteosarcoma is extremely difficult to produce in rats; the only other environmental agent known to induce osteosarcoma in rats is high doses of radiation;

- The levels of fluoride in the treated rats' bones were in the same range as fluoride found in human bones;

- Bones are the site of fluoride accumulation, and;

- The osteosarcomas were evident before the end of the study, indicating an age dependent vulnerability similar to that seen in human males.

The study authors were unequivocal about their findings: "The neoplasms were clearly malignant (one metastasized to the lung) and there was complete agreement concerning the diagnoses at both the quality assessment and Pathology Working Group stages of the histopathology review."

Curiously, a 1993 National Research Council (NRC) review appeared to miss the importance of the findings. In characterizing the significance of the findings the NRC stated simply: "The equivocal result of osteosarcoma in male rats was not supported by results in females in the same study" (NRC 1993). This is an extraordinary statement given the prescient concerns for young males raised 16 years earlier by the NAS (in 1977), and the available epidemiologic data available at that time (Hoover 1991; Cohn

1992). Increased osteosarcoma in males, as identified in the Hoover and Cohn studies, is precisely the result that the 1977 NAS panel was concerned about.

In a 2002 review of fluoride toxicity the World Health Organization offered a more reasoned assessment of the results of the NTP rat study: "Such a (dose-dependent) trend associated with the occurrence of a rare tumour in the tissue in which fluoride is known to accumulate cannot be casually dismissed" (WHO 2002).

An additional animal study was conducted by Procter & Gamble, using both mice and rats. The study found a large, dose-dependent increase in rare bone tumors (osteomas) in fluoride-treated mice (Maurer 1993). The second part of the study, in rats, again found bone tumors and a rare tooth tumor in the treated rats but not the controls (Maurer et al. 1990). Apparently this study was discounted because most of the tumors, although rare, were not yet malignant.

**Fluoride causes genetic damage in humans**

A compound's ability to cause genetic damage is considered an important indicator of cancer-causing potential. Many studies have investigated and found positive evidence of fluoride's genotoxicity. Notable among these is a 1996 study that reported that sodium fluoride was mutagenic to rat cortical bone, the same tissue in which osteosarcoma forms (Mihashi and Tsutsui 1996).

Since 1994, six of eight published genotoxicity studies have found an increased incidence of genetic damage in humans exposed to fluorides. Three were from exposure to airborne fluorides (Meng 1995, 1997; Lazutka 1999), and three others from exposure to fluoride in drinking water (Sheth 1994; Wu 1995; Joseph 2000). In two of the three drinking water studies (Sheth 1994 and Joseph 2000) exposure levels were well within legal limits for fluoride in tap water in the United States (1.9 - 2.2 parts per million (ppm) and 1.6 - 3.5 ppm respectively). The third was at 4 to 15 ppm. Two?additional studies reported no increase in mutagenic damage or decrease in damage among humans drinking excess fluoride in water (Li 1995; Jackson 1997).

The most commonly observed genetic effect has been increased sister-chromatid exchange (SCE), a measure of how often the ends of DNA strands break off and the pieces switch positions when they reattach themselves (see: Sheth 1994; Meng 1995, Wu 1995; Lazutka 1999; Joseph 2000). Wu, who found an increase of SCE among humans drinking water with 4 - 15 ppm fluoride, described the significance of SCE as follows:

> "In recent years, SCE analysis has been considered to be a sensitive method for detecting DNA damage. There is a clear relationship between a substance's ability to induce DNA damage, mutate chromosomes, and cause cancers. The SCE frequency in the human body in peripheral blood lymphocytes is very steady, and does not vary with age or sex. Any increase of the SCE frequency is primarily due to chromosome damage. Thus using a method to detect SCE for exploring the toxicity and harm caused by fluoride is of great importance" (Wu 1995).

The finding of increased SCE in fluoride-exposed humans has reinforced the possibility — as suggested by numerous in vitro studies — that fluoride is a mutagenic agent.

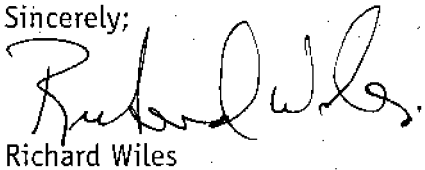
*Human sensitivity*

The mutagenicity of fluoride was compared in cells taken from rodents with the mutagenicity of fluoride in cells taken from great apes and humans (Kishi 1993). The conclusion of the study was that the ape and human cells showed greater susceptibility to fluoride's mutagenic effects than the rodent cells. These findings suggest that humans may be more susceptible to fluoride's mutagenic properties, and consequently, more susceptible to a potential carcinogenic effect. They may also explain the findings of mutagenic damage in humans' drinking water with relatively low fluoride concentrations: 1.9 - 2.2 ppm and 1.6 - 3.5 ppm (Sheth 1994; Joseph 2000).

**Recommendations**

The safety of fluoride in America's tap water is a pressing health concern. More than 170 million people live in cities and towns with fluoridated water, and the weight of the evidence strongly supports the conclusion that millions of boys in these communities are at significantly increased risk of developing bone cancer as a result. EWG urges the National Toxicology Program to put fluoride into an expedited review for inclusion in its Report on Carcinogens.

Sincerely;



Richard Wiles
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Environmental Working Group

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