Appendix 1-A. FAN submission to NRC 2006 on cancer, Part 1

Revisiting the Fluoride-Osteosarcoma connection in the context of Elise Bassin's findings: Part I

by

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1. Introduction

In April of 2001, a critically important addition to the scientific literature on fluoride and osteosarcoma was produced, in the form of a PhD dissertation, at Harvard University (Bassin, 2001). Due to difficulties in obtaining access to this work, we have only recently been able to assess its importance. The thesis, authored by Dr. Elise Bassin, found a strong statistically significant relationship between fluoride exposure during the 6th to 8th years of life (the "mid-childhood growth spurt") and the later development of osteosarcoma among young males.

Her study utilized two important improvements in methodology over all previous studies.

First, she looked at age-specific exposure instead of cumulative lifetime exposure or "snapshot" time-of-diagnosis exposure. While previous papers have pointed to the biological plausibility of fluoride inducing osteosarcoma during a narrow "window of vulnerability", Bassin is the first author to analyze her data in a manner capable of detecting the "window."

Second, Bassin improved the accuracy of fluoride exposure assessment for her subjects by using more detailed methods of ascertaining the actual fluoride content of drinking water for individual subjects (Bassin 2004).

If Bassin's methods and findings are applied to the interpretation of earlier studies, we believe they may explain why several researchers were not able to detect an association between fluoride and osteosarcoma. Bassin's work effectively reopens the entire question of fluoride's carcinogenicity and gives strong new evidence that it is in fact a carcinogen.

Bassin herself gives a good overview of the topic of osteosarcoma and fluoride:

> Osteosarcoma is an uncommon but highly lethal primary malignant tumor of bone (Dorfman and Czerniak, 1995) associated with a median survival of approximately three years (Homa et al., 1991). The etiology of osteosarcoma is essentially unknown (Link and Eilber, 1997). It develops from primitive bone-forming mesenchyme within bone and is characterized by the production of osteoid tissue (Link and Eilber, 1997). Although osteosarcoma is very rare, it is the most common tumor of bone and one of the principal malignant neoplasms in children, adolescents and young adults (Homa et al., 1991; Dorfman and Czerniak, 1995; Link and Eilber, 1997), with an incidence rate of 5.6 per million per year for Caucasian children under 15 years old (Link and Eilber, 1997). Males are affected 1.5 to 2 times as frequently as females (Link and Eilber, 1997; Dorfman and Czerniak, 1995) and their survival from time of diagnosis tends to be shorter than for females (Homa et al., 1991). The age-incidence distribution of osteosarcoma is bimodal raising the possibility of different risk factors contributing to the incidence of osteosarcoma at different ages. The first and larger peak incidence occurs in the second decade of life (Fraumeni, 1975; Link and Eilber, 1997; Dorfman and Czerniak, 1995). Most but not all evidence suggests osteosarcoma is associated with growth (Johnson, 1953; Price, 1958; Tjalma, 1966; Fraumeni, 1967; Operskalski et al., 1987; Link and Eilber, 1997; Henderson et al., 1997; Gelberg et al., 1997; Buckley et al., 1998; Re et al., 1998). Since fluoride acts as a mitogen (increasing the proliferation of osteoblasts) and its uptake in bone increases when skeletal growth is more rapid, (Gruber and Baylink, 1991; Ganong, 1995; Kleerekoper, 1996; Whitford, 1996), it is biologically plausible that fluoride exposure during specific periods of growth is associated with the subsequent development of osteosarcoma, and fluoride could either increase or decrease the rate of osteosarcoma.
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> – Bassin (2001) p. 68.

Like Bassin, we feel it is important to stress the biological plausibility of fluoride's ability to cause osteosarcoma. There are three key acknowledged mechanisms supporting a fluoride/osteosarcoma connection. First, the preponderance of laboratory evidence indicates that fluoride can be mutagenic when present at sufficient concentrations (NTP 1990; Bassin 2001). Many mutagens are also carcinogens. Second, the bone is the principal site for fluoride accumulation within the body, and the rate of accumulation is elevated during periods of bone development. Thus, the cells in the bone, particularly during the growth spurts, may be exposed to some of the highest fluoride concentrations in the body. Third, fluoride is a 'mitogen' - meaning it can stimulate the proliferation of bone-forming cells (osteoblasts). Osteosarcoma is a cancer caused by an abnormal proliferation of the osteoblasts. Hence, fluoride's ability to induce mutagenic damage in fluoride-rich environments, coupled with its ability to stimulate proliferation of osteoblasts, provides a compelling biological basis by which fluoride could cause, or contribute to, osteosarcoma. Here are some relevant quotes from the literature:

> **... it would appear that sodium fluoride is genotoxic in a number of genetic toxicity assays,** through as yet undetermined mechanisms. **So, a neoplastic effect in a tissue that accumulates fluoride would appear possible.**
>
> – Bucher (1990) p. 30-31. [See: www.fluoridealert.org/health/cancer/mutagen]

> ... if fluoride were to exert a neoplastic effect, it is reasonable to expect that this might be expressed in a tissue that accumulates fluoride. This would include bone, and, therefore,

there is biological plausibility for an association between sodium fluoride administration and the development of bone osteosarcomas.
– National Toxicology Program [NTP] (1990).

When fluoride exposure increases, the following bone responses generally occur: 1) an increase in the number of osteoblasts, 2) an increase in the rate of bone formation, 3) an increase in the serum activity of alkaline phosphatase, and 4) an inhibition of osteoblastic acid phosphatase.... **The increase in osteoblast proliferation and activity may increase the probability that these cells will undergo malignant transformation.**
– Gelberg (1994) p. 13.

The results indicate that NaF is genotoxic to rat vertebrae, providing a possible mechanism for the vertebrae, as a target organ of NaF carcinogenesis.
– Mihashi & Tsutsui (1996).

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. First, approximately 99 percent of fluoride in the human body is contained in the skeleton with about 50 percent of the daily ingested fluoride being deposited directly into calcified tissue (bone or dentition). Second, fluoride acts as a mitogen, increasing the proliferation of osteoblasts and its uptake into bone increases during periods of rapid skeletal growth.
– Bassin (2001) p. 79.

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.
– World Health Organization [WHO] (2002).

[bold text is our emphasis]

The biological plausibility for a fluoride-osteosarcoma relationship combined with Bassin's recent findings highlight the need to reexamine previous studies.

2. Bassin's methods and findings

Bassin used a database of osteosarcoma cases and matched controls taken from 11 hospitals around the USA between 1989 and 1992. Controls were matched by age (±5 years), sex, and approximate residence distance from hospital. She analyzed data for subjects aged 20 years and younger at diagnosis. Covariates examined were:

1) socioeconomic status
2) county population size
3) whether subjects ever drank bottled water or well water
4) age at study entry because age matching was only to within ±5 years
5) whether subject had exposure by self-administered or school administered fluoride products.

As mentioned above, Bassin is the first to examine age-specific fluoride exposures. To date, this is the only study on cancer and fluoride to do so. All others have looked at exposure at time of diagnosis, cumulative lifetime exposure, average lifetime exposure, or exposure over broad time periods. An age-specific association between bone cancers and fluoride had been postulated at least as early as 1992 by Cohn and was repeated by Lee in 1993 and 1996.

> If rapidly growing bone in adolescent males is most susceptible to the development of osteosarcomas (Glass and Fraumeni, 1970), **it is possible that fluoride acts as a cancer promoter during a narrow window of susceptibility**. The interplay of hormonal influences and the intensity of the growth spurts may be potent influences. Since fluoride is toxic to cells and a variety of enzymes at high concentrations (reviewed by Kaminsky et al., 1990; and Public Health Service, 1991), it may exert tumor promoting effects in the osteoblast cell microenvironment during bone deposition. Genetic predisposition may also play a role.
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> – Cohn (1992) p. 11.

Lee (1993) applied this concept to Hoover's 1991 work:

> As noted by Dr Cohn, the etiology of osteosarcoma has not been established. The fact that rapidly growing bone in adolescent males is most susceptible to the development of osteosarcoma suggests that fluoride, which is known to be toxic to bones and a potent enzyme inhibitor, may act as a cancer promoter during this narrow window of susceptibility. Given this, the available SEER epidemiologic data [used by Hoover 1991] may be more significant than appreciated by the PHS which discounted the observed fluoride/osteosarcoma correlation on the basis of the absence of a linear trend of association with duration of time the water supplies were fluoridated. However, **if fluoride acts as a cancer promoter, rather than an initiator, the duration/latency assumption is not warranted**.
>
> – Lee (1993) pp. 80-81.

Lee (1996) returned to this point that organisms may be more sensitive to a carcinogen at certain developmental stages in their lives. The following is from his review of Gelberg's 1995 paper:

> In testing the fluoride/osteosarcoma link, **one must be able to calculate total fluoride intake at various stages of life preceding the onset of the cancer.**
>
> – Lee (1996) p. 238.

In addition to being the first to utilize the age-specific approach to assess the fluoride/osteosarcoma risk, Bassin also used a more refined methodology for assessing fluoride intake than in previous studies (Bassin 2004).

Instead of making assumptions about the fluoride level in private well water, she actually took water samples and made laboratory measurements. Instead of relying solely on the CDC Fluoridation Census to assess fluoride level in municipal water, she double-checked with individual state or local health and water departments to confirm

the fluoride level in water supplied to her subjects' residences for each year of life. Bassin is also the first to carefully assess bottled water's contribution to fluoride exposure. She found by research that the ten most popular brands of bottled water averaged about 0.1 ppm F. Furthermore, she took into account the fact that even people who drink bottled water will often use tap water for cooking and will be consuming other drinks outside their home. For bottled water drinkers, she assigned half their fluid intake to bottled water and the other to their tap water. Overall, compared to other studies, Bassin's fluoride exposure assessment methodology is likely to be more accurate and lead to fewer misclassification errors. This increases the power of her analysis to detect an association between fluoride and osteosarcoma.

From interviews with cases and controls, she determined what their drinking water sources were for each year of their lives. She then calculated their fluoride consumption level for that year and assigned subjects to one of three categories:

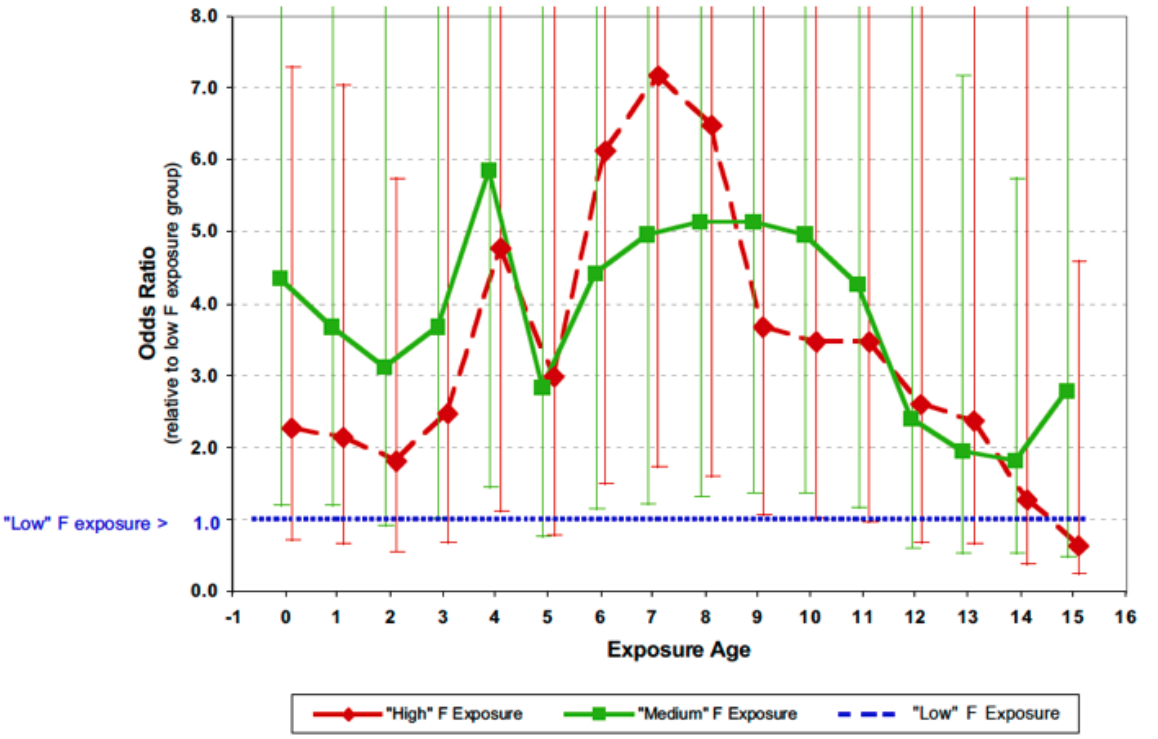
"Low" with less than 30% of "optimal" F
"Medium" with 30 to 99% of "optimal" F
"High" for those drinking 100% or more of "optimal" F levels.

"Optimal" fluoride level is as determined by climate and averages 1.0 ppm for the US.

Using conditional logistic regression to maintain matching, Bassin calculated the Odds Ratio (OR) for each age of exposure for the "Medium" and "High" exposure compared to "Low" fluoride exposure. She found that among males, for almost all ages of exposure, there was an increased risk. In particular, for ages 6, 7, and 8 there was a peak in risk, which was statistically significant at the 95% Confidence Interval (CI) level. For her model with covariates the peak risk for exposure occurred at age 7 and reached an OR of 7.2 (CI 1.7-30.0). We have redrawn Bassin's Fig. 3.2A graph converting the logarithm of the Odds Ratios to straight Odds Ratios for easier interpretation. It is noteworthy that even for the "Medium" exposure category the risk was consistently greater than 1.0. Moreover, the majority of the "Medium" exposure ages reached statistical significance.

Bassin interprets her finding that both "Medium" and "High" exposure groups showed similar elevated risk as evidence of a possible threshold effect instead of the more commonly assumed dose-response relationship between fluoride and osteosarcoma. If true, her data suggests that the threshold concentration could be as low as 0.3 ppm fluoride in drinking water.

From Bassin Fig 3.2A Odds Ratios for age-specific fluoride exposure, males, based on model with covariates (Beta converted to Odds Ratio)



Our version of Bassin's Fig. 3.2A was created by digitally measuring the values in her graph and converting them from logarithms of Odds Ratios to straight Odds Ratios for easier interpretation. The error bars represent the 95% Confidence Interval. Odds Ratios above 1.0 represent increased risk from fluoride exposure relative to the baseline "Low" exposure group. Values below 1.0 represent decreased risk.

Bassin presents the ORs for each age of exposure up to age 15 but does not calculate the lifetime Odds Ratio for a subject who lived their entire life drinking water at the "Medium" or "High" exposure level. Nevertheless, a rough estimate can be made by averaging the age-specific ORs up through the age of diagnosis. For a child diagnosed at age 15 their lifetime OR would be about 4.

Bassin summarizes her findings as "remarkably robust":

> Our exploratory analysis describes the association of fluoride level in drinking water and osteosarcoma at specific ages. It suggests that **for males less than twenty years old, fluoride level in drinking water during growth is associated with an increased risk of osteosarcoma, demonstrating a peak in the odds ratios from ages six to eight years of age (OR=7.20, 95 percent CI 1.73-30.01 at age 7). All of our models are remarkably robust in showing this effect during the mid-childhood**

> **growth spurt**, which, for boys, occurs at ages seven and eight years (Molinari et al., 1980; Tanner and Cameron, 1980; Berkey et al., 1983; Tanner, 1990).
> – Bassin (2001) p. 76.

Bassin concludes by suggesting that ongoing and future studies consider incorporating age-specific exposure analysis. She also explains why failure to look at age-specific exposure will tend to obscure evidence of an association between fluoride and osteosarcoma.

3. A re-examination of other osteosarcoma studies in light of Bassin's findings

In her introduction, Bassin describes some of the conflicting data surrounding a possible fluoride-osteosarcoma connection. She writes:

> There are conflicting data regarding the association between fluoride exposure and the incidence of osteosarcoma. Several animal studies have been conducted, but only one has shown that exposure increases osteosarcoma formation, specifically in male rats (Bucher et al., 1991). Human studies also show conflicting results. The majority of epidemiological studies found no association between fluoride and osteosarcoma (Hrudey et al., 1990; Mahoney et al., 1991; Freni and Gaylor, 1992; Operskalski et al., 1987; McGuire et al., 1991; Moss et al., 1995; Gelberg et al., 1995). However, an association between fluoride in drinking water and osteosarcoma was noted in males under age twenty in two prior studies (Hoover et al., 1991; Cohn, 1992), while no association has been observed in females or among cases occurring at older ages. Furthermore, prior studies have primarily evaluated fluoride exposure at the time of diagnosis or as an average lifetime exposure and have not evaluated exposure at specific ages during growth and development when cell division is occurring rapidly.
> – Bassin (2001) pp. 68.

In her discussion section, Bassin explains how her findings are consistent with several previous studies:

> Our results are consistent with findings from the National Toxicology Program animal study which found "equivocal evidence" for an association between fluoride and osteosarcoma for male, but not female, rats (Bucher et al, 1991) and from two ecological studies that found an association for males less than twenty years old (Hoover et al., 1991; Cohn, 1992). Using data from the Surveillance, Epidemiology and End Results (SEER), Hoover et al. found an unexplained increase in osteosarcoma in males under 20 years of age in fluoridated versus non-fluoridated areas, but an analysis which took into account the duration of fluoride exposure failed to demonstrate a relationship between fluoride and osteosarcoma (Hoover et al., 1991). A similar, but much smaller study conducted in New Jersey also showed an increase in osteosarcoma incidence rates for males less than 20 years old who lived in fluoridated areas compared to those living in non-fluoridated areas (Cohn, 1992).
> – Bassin (2001) pp. 77-78.

But Bassin also acknowledges that her work conflicts with the findings of other studies and offers these explanations as to why this may be the case:

> A number of other case-control studies did not find an association between fluoride in drinking water and osteosarcoma (Operskalski et al., 1987; McGuire et al., 1991; Moss et al., 1995; Gelberg et al.; 1995). One possible reason for the lack of agreement may be related to the bimodal age-incidence distribution of osteosarcoma (Dorfman and Czerniak, 1995). When there are two distinct peaks in an age-incidence distribution, it has been suggested that two distinct sets of component causes should be considered (MacMahon and Trichopoulous, 1996). McGuire et al. (1991) and Moss et al. (1995) included cases up to age forty years and age eighty-four years, respectively, and if fluoride exhibits a different effect according to the age-specific distribution, detecting an effect would be unlikely. The study by McGuire et al. (1991) was also very small with only 22 cases of osteosarcoma. In another study of osteosarcoma in young people, researchers selected friends and neighbors as controls (Operskalski et al., 1987). Although this choice of selection might have been optimal for some exposures of interest, it resulted in inadvertently matching on fluoride exposure in drinking water, so as a result of overmatching, detecting a benefit or risk for fluoride would be unlikely.
>
> Another potential explanation for the lack of similar findings reported in other studies which did not find an effect is that we evaluated age-specific effects. Rothman (1981) has pointed out that failure to identify the appropriate time window for exposure may result in misclassification which can adversely affect the ability to detect an association. This might explain why the study by Gelberg et al. (1995) did not find an association between fluoride in drinking water and osteosarcoma since age-specific effects were not evaluated.
>
> – Bassin (2001) pp. 77-78.

Underscoring the limitations of earlier analyses, it bears emphasizing that Bassin's work is based on the same data used by an earlier study that had reported no association between fluoride and osteosarcoma (McGuire, Douglass, et al. 1995). Unlike the 1995 analysis of this dataset, Bassin 1) excluded all patients diagnosed after the age of 20 and 2) assessed the risk as a function of fluoride exposure for each year of life. In so doing, Bassin's work shows that the initial 1995 analysis had obscured an important age-specific effect.

Again, the difference in results obtained by McGuire, Douglass et al.1995 and Bassin 2001, using the same set of data, illustrates the importance of revisiting the earlier analyses. We will be doing this in Part II of our submission.

The following studies, constituting virtually all recent work on osteosarcoma and fluoride, will be addressed in more detail in Part II:

Case-control studies	**Ecological studies**
McGuire et al. (1991)	Mahoney et al. (1990)
Moss et al. (1995)	Hrudey et al. (1990)
Gelberg (1994)	Hoover et al., appendix F, DHHS (1991)
Gelberg et al. (1995)	Hoover et al., appendix E, DHHS (1991)
McGuire, Douglass et al. (1995)	Cohn (1992)
	Freni and Gaylor (1992)
	Yiamouyiannis (1993)
	Takahashi et al. (2001)

4. Discussion and Conclusions

If we consider Bassin's findings in terms of everything that has taken place in this area of research, there is now a clear pattern of association between osteosarcoma and fluoride exposure in young men stretching back to early conjecture in 1956. Here is a summary of that pattern.

4.1 Before any animal or epidemiological study had been undertaken on osteosarcoma and fluoride exposure, conjecture about such a relationship was published in 1977 by the National Academy of Sciences (NAS). Their comments were based upon the pattern of cortical bone defects observed in one of the first trials of water fluoridation in the US which took place in Newburgh-Kingston, NY (Schlesinger et al. 1956). Of particular interest is that the NAS specifically highlighted **young males** as the target population of concern. NAS authors wrote:

> There was an observation in the Kingston-Newburgh (Ast et al, 1956) study that was considered spurious and has never been followed up. There was a 13.5% incidence of cortical defects in bone in the fluoridated community but only 7.5% in the non-fluoridated community... Caffey (1955) noted that the age, sex, and anatomical distribution of these bone defects are 'strikingly' similar to that of osteogenic sarcoma. While progression of cortical defects to malignancies has not been observed clinically, **it would be important to have direct evidence that osteogenic sarcoma rates in males under 30 have not increased with fluoridation.**
>
> – NAS (1977)

4.2 A relationship between osteosarcoma in bone and fluoride exposure in young males is biologically plausible because 1) fluoride accumulates in bone and the accumulation rate is elevated during periods of active bone development (e.g. growth spurts); 2) fluoride is a recognized mitogen that can increase the proliferation of osteoblasts (bone-forming cells), possibly by stimulating G-proteins; 3) bone growth is influenced by hormonal status thus it is not unlikely that we will observe different effects in males and females; 4) fluoride has been shown to be mutagenic in several species, including humans, and in tissue lines.

4.3 The fact that the animal studies conducted by the NTP did find a dose related increase in osteosarcomas in male rats but not in the female rats, in our view, unlike the NRC (1993) interpretation, **strengthens rather than weakens the case.** It also needs to be stressed that osteosarcoma in animals is very difficult to generate by chemical means. It bears mentioning also that osteosarcomas, and other forms of bone cancer, were observed in the treated animals of the Proctor and Gamble studies (FDA 1990) although not in a dose-dependent manner or at statistically significant rates. Osteomas (benign bone tumors) on the other hand, were found at increased rates in higher dosed

animals and a panel of FDA reviewers concluded that they were significantly associated with fluoride exposure (FDA 1990).

4.4 Being a rare cancer in humans, an ecological study would need to be particularly large to find this relationship, or a case-control study particularly well designed to find it. We will look at each of these in turn.

4.5 Large Ecological studies:

4.5.1 Hoover et al. (1991) did find an association between fluoridation and osteosarcoma in some of their analyses. Other methods of analyzing their data did not reveal expected dose-response relationships. A re-examination of Hoover's methods and results in the context of our current understanding of the age-specific nature of the risk could explain his contradictory findings.

4.5.2 We believe that Takahashi et al. (2001) were able to uncover the relationship by investigating virtually the entire SEER data base, using a more realistic index of fluoride exposure than previous studies. They assessed exposure based upon the percentage of the population fluoridated. Most previous studies used only a simple yes/no classification scheme based on a region having above or below a certain percentage of fluoridation.

4.5.3 We believe that Freni and Gaylor (1992) may have found it in their comparative international study had they known more accurately which countries were fluoridated and which were not.

4.5.4 We believe that if all the large ecological based data is re-examined using the innovative approach of Yiamouyiannis (1993), who used female osteosarcoma cases as a control for variables other than fluoridation status, that again the relationship may become apparent.

4.6 However, as Bassin points out, the relationship in the large ecological studies is easily lost if all age ranges are included or both sexes are examined together.

4.7 In light of Bassin's finding that the "window of vulnerability" is the critical parameter of concern, it is possible that when earlier case-control studies are revisited, their negative findings will be explained, as in the study by Gelberg et al. (1995). This possibility needs to be taken very seriously, particularly since Bassin's analysis used the same case-control data that an earlier team of authors had analyzed in a 1995 study reporting no effect.

In general, all studies which either fail to address age-specific exposures or which use poor methods for assessing fluoride exposure will result in greater non-differential misclassification of subjects. Such misclassification will tend to weaken the power of the study to find an association between fluoride and osteosarcoma. Coupling this with

the rarity of the cancer and the small numbers of cases in most studies, may explain why many of the studies to date have not found an association.

Thus, when previous results are re-examined in the light of Bassin's findings, and considering the acknowledged biologic plausibility of a fluoride-osteosarcoma link, the balance must shift to a conclusion that the preponderance of evidence indicates a positive relationship between osteosarcoma in young men and exposure to fluoride. The critical ages for exposure appear to be their 6th, 7th, and 8th years, i.e. during a window of vulnerability when young boy's mid-childhood bone growth spurt is taking place.

Such a conclusion would suggest a recommendation for a Maximum Contaminant Level Goal (MCLG) of zero, since according to the US EPA there is no safe level for a chemical considered a human carcinogen. Clearly, a compromise will be needed for a realistic Maximum Contaminant Level (MCL), because of the costs of removing natural fluoride. Fortunately, neither that discussion nor that compromise need concern the NRC panel, since their brief is to advise on the best science to inform an appropriate MCLG.

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