

From: Paul Connett  
To: <coshita@oehha.ca.gov>  
Date: 5/4/2009 9:57 AM  
Subject: Proposition 65  
Attachments: California-osteosacoma.doc

To: coshita@oehha.ca.gov

Subject: Comments on behalf of adding fluoride chemicals and cancer to Proposition 65

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

Dear Ms. Oshita and all concerned,

I would like to take this opportunity to provide a narrative to put into context the possibility that fluoride and fluoridation may contribute towards an increase in osteosarcoma in young men and possibly other bone cancers.

Other members of the Fluoride Action Network will be forwarding a far more formal and in-depth summary of some of the key studies you should be examining. I provide this summary to put the whole issue into perspective and hopefully it can be used to support a <sup>3</sup>weight of evidence<sup>2</sup> analysis which would indicate that fluoride is a probable human carcinogen. The narrative also makes clear that there is a huge amount of politics operating here. Those who promote water fluoridation do so with a zeal which is unimaginable to the ordinary person or scientist. Clearly for them a fluoride-osteosarcoma connection would completely undermine water fluoridation. So promoters in government have gone to some pretty extraordinary lengths to discredit any study or any scientist who has the temerity to suggest such a connection. Please therefore do not be trapped into making a judgment on this matter on the basis of <sup>3</sup>authority<sup>2</sup> - whether that authority is the US Public Health Service (including the CDC), the NCI or the ADA - on this issue it is highly suspect. Please judge this issue only on its scientific merits.

I hope you find this narrative and documentation helpful and that you will add fluoride chemicals to Proposition 65.

Sincerely,

Paul Connett, PhD,  
Professor Emeritus Environmental Chemistry,  
St. Lawrence University,  
Canto, NY 13617

And

Executive Director,  
Fluoride Action Network

## Fluoride and osteosarcoma

### Observations in 1955

There were observations on cortical bone defects observed in the Newburgh-Kingston study (1945-55) prompted Donald Taves to make the following comment in a report published by the National Academies of Science in 1970:

"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." (our emphasis).

Osteogenic sarcoma, now called osteosarcoma, is a rare but frequently fatal bone cancer.

This observation by Caffey in 1955, and underlined by Taves in 1970, was the beginning of long history of the possibility that fluoridation may increase the incidence of osteosarcoma in young men. Before we get to that history, we will first look at the "biological plausibility" of a fluoride-osteosarcoma link, which is widely acknowledged in the scientific literature.

### Biological plausibility

The 3 key findings supporting the plausibility of a fluoride/osteosarcoma connection are:

- 1) The bone is the principal site for fluoride accumulation within the body, and the rate of accumulation is increased 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.
- 2) The preponderance of laboratory evidence indicates that fluoride can be mutagenic given sufficiently high concentrations (most mutagens are carcinogens) cause chromosome damage and interfere with the enzymes involved with DNA repair in a variety of cell and tissue studies (Tsutsui 1984; Caspary 1987; Kishi 1993 and Mihashi 1996). Recent studies have also found a correlation between fluoride exposure and chromosome damage in humans (Sheth 1994; Wu 1995; Meng 1997 and Joseph 2000).
- 3) 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.

Thus, 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.

According to the authors of the NRC (2006) report:

“Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in non-dividing states.” (NRC, 2006, p.275)

According to Bassin (2006):

"It is biologically plausible that fluoride affects the incidence rate of osteosarcoma, and that this effect would be strongest during periods of growth, particularly in males. First, approximately 99% of fluoride in the human body is contained in the skeleton with about 50% 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 in bone increases during periods of rapid skeletal growth. In the young, the hydroxyapatite structure of bone mineral exists as many extremely small crystals each surrounded by an ion-rich hydration shell, providing a greater surface area for fluoride exchange to occur."

### **An historical overview of fluoride and osteosarcoma (1990 – 2009)**

After the observations of Caffey (1955) and the recommendation based upon them by Donald Taves (NAS, 1970) that rates of osteosarcoma **in males under 30** be investigated in fluoridated communities, it took another 20 years before this suggestion was followed. Meanwhile, in the 1970's Dr. John Yiamouyiannis, a biochemist, and Dr. Dean Burk, former head of the Cytochemistry Section of the National Cancer Institute, stirred up a hornet's nest when they published a study claiming a greater increase in cancer rates after fluoridation was introduced into 10 US cities compared to 10 other US cities which were not fluoridated.

Robert Hoover and others at the National Cancer Institute attempted to rebut these findings and they were soon joined by several other epidemiologists including Kinlen and Sir Richard Doll in the UK who claimed to have looked at the same data and found no such relationship. However, the furor generated led to full scale Congressional hearings, which took place in 1977.

After listening to both sides in this debate, Congress ordered animal studies to determine whether fluoride causes cancer under laboratory conditions. The National Toxicology Program (NTP), under the U.S. Public Health service, commissioned Battelle Memorial labs to do these studies. Oral, liver and bone cancer received special attention. The results, which should have been completed and released in 1980, were not finally released until 1990.

## **NTP animal study (1990)**

Battelle found several cancers but they were all downgraded (see below) except osteosarcoma. The Battelle researchers found a dose-related increase in osteosarcoma in MALE (but not female) rats exposed to fluoride (Bucher et al., 1990; Bucher et al., 1991 and DHHS, 1991). After reviewers had removed one of the osteosarcomas, this finding was classified as “equivocal evidence of cancer.”

Commenting on these NTP findings a committee from the World Health Organization (WHO) made the following comment:

"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)

Later, in 1996, Mihashi and Tsutsui lent further credibility to the NTP result, when they were able to demonstrate that fluoride caused chromosomal aberrations in a time and dose dependent manner in cultured cells derived from the vertebral bones of the same strain of rats (F344/N) used in the NTP rat study. Effects were observed at 4.3 ppm fluoride, a level which can be anticipated in key microenvironments in the bone in vivo. They argued that their results, “demonstrate that NaF is clastogenic to rat vertebral body-derived cells, providing a mechanistic basis for NaF to induce osteosarcomas in NaF-treated rats.”

## **Other cancers found in NTP study**

The NTP study also reported an increase in a liver and oral cancers, and an increase in the incidence of thyroid follicular cell tumors. However, a government-review panel downgraded all the non-bone cancers with a questionable rationale (Marcus 1990). One of the cancers downgraded was a rare form of liver cancer called hepatocholangiocarcinoma. The peer reviewers examining the slides claimed that this was not hepatocholangiocarcinoma but Dr. Melvin Reuber, an independent pathologist formerly with the National Cancer Institute, who was the first to describe this rare form of liver cancer, concurred with the pathologist at the Battelle Memorial Laboratory that this was indeed a case of hepatocholangiocarcinoma. In light of the importance of this study, the union representing professionals working at the EPA headquarters in Washington, DC, has requested that Congress establish an independent review to re-examine these cancer slides (Hirzy 2000). Meanwhile, the NTP finally prompted the National Cancer Institute to review osteosarcoma rates in fluoridated communities in the US (which Taves had recommended 20 years earlier in 1990, see above).

## **Department of Health and Human Services (DHHS)**

The NTP study results were first made public in a report from the Department of Health and Human Services (DHHS) entitled *Review of Fluoride: Benefits and Risks*, published in February 1991. This same report also contained in Appendices E and F an analysis of the SEER registries by the Robert Hoover et al. from the National Cancer Institute (NCI) which we will discuss next.

## **NCI Survey of the SEER registries for osteosarcoma (1991)**

The National Cancer Institute (NCI) examined the nine SEER cancer registries (which cover about 10% of the US population) for bone cancer. The NCI found a greater increase in osteosarcoma in young **males** (but not for young females) in fluoridated versus non-fluoridated counties (Hoover et al, 1991 a)) However, the same authors, using a subset of the data claimed that they did not find that this increase was related to duration of exposure and discounted the original finding (Hoover et al., 1991 b).

Today, more credibility is given to Hoover' et al.'s first finding (Hoover et al., 1991 a) than their second (which supposedly discounted the first). This is largely because by the time the NCI authors had used a subset of the data and divided it between 4 different age ranges of exposure, there were so few cases left in each grouping that the study lacked any statistical power (Hoover et al., 1991 b). However, at the time their second finding certainly helped fluoridation promoters to downgrade concern on this issue.

Later, both Yiamouyiannis (1993) and Takahashi (2001) examined the same data base used by Hoover et al. and found a significant increase in osteosarcoma in young males in fluoridated counties.

## **McGuire et al., 1991**

A small study published in the April 1991 issue of the Journal of the American Dental Association, warning that a finding of a relationship between fluoridation and osteosarcoma would threaten the water fluoridation program, reported that fluoride might actually be *protective* against osteosarcoma. One of the co-authors of this study was Professor Chester Douglass from the Harvard Medical School (see more below).

## **Cohn, 1992**

In 1992, Cohn, working for the NJ Health department, reported a significant increase in osteosarcoma in young **males** in the fluoridated communities in three NJ counties – but again not for young females (Cohn, 1992). Most significantly Cohn suggested that there might be a time frame where young boys are particularly vulnerable to fluoride's carcinogenic effect. Cohn wrote:

“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.” (Cohn ,1992, p. 11.) (our emphasis)

## **Other studies**

Other epidemiological studies of various sizes and quality have failed to find this relationship (Hrudy, 1990; Mahoney 1991; Freni, 1992; McGuire, 1991; Gelberg, 1995; Moss, 1995). For a full review of these studies and other studies on osteosarcoma see the submission to the National Research Council by the Fluoride Action Network (Connett, Neurath and Connett, 2005 a and b).

### **Elise Bassin, 2001**

Elise Bassin is a dentist. She investigated a possible relationship between exposure to fluoride and osteosarcoma as part of her PhD thesis at the Harvard Dental School. Suspecting a possible time window of vulnerability for this problem (as Cohn had conjectured it might, see above) Bassin examined osteosarcoma rates as a function of which years the boys were exposed to fluoride.

In a matched case-control study, Bassin found, in what she herself described as a “robust finding,” that young boys exposed to fluoride in their 6th - 8th years (which corresponds to the mid-childhood growth spurt) had a 5 to 7 fold increased risk of succumbing to osteosarcoma by the age of 20. Her thesis was successfully defended in 2001 (Bassin, 2001).

### **Bassin’s PhD thesis hidden from the scientific community**

It is extraordinary that after Bassin’s thesis was successfully defended in 2001, that it was neither followed up with a swift publication of her results nor any kind of statement made to warn the scientific community or the public about her findings. After all, if she was correct, a chemical being given daily to over 170 million Americans in their drinking water, might actually be killing people! If this discovery had been made by industrial researchers on an industrial chemical and the authors had hidden the findings from government regulators they would have been in serious trouble.

### **Professor Chester Douglass**

Professor Chester Douglass was Bassin’s thesis adviser and signed off on her thesis in 2001. Clearly, he knew what she had found and knew the serious implications of her findings. A paper on the same subject that Douglass had co-authored makes this abundantly clear (McGuire et al., 1991). However, even though he was given several opportunities to do so, Douglass neither warned his colleagues in professional meetings (e.g. a meeting organized by the British Fluoridation Society in 2002), nor the NRC panel nor his funders at the NIH (NIEHS had put over \$ 1 million financing Douglass’ work). Instead of warnings he did the very opposite. He continued to assert that “his” work showed no significant association between fluoride and osteosarcoma. In his written comments to the NRC panel he even gave Bassin’s thesis as a footnote, but without indicating that her findings contradicted what he was telling the panel.

### **Bassin’s thesis discovered**

Finally, Michael Connett, of the Fluoride Action Network, acting on a tip off, went to the Harvard Medical School Rare Books Room in January 2005 and “discovered” the “hidden” thesis. The resulting public release of this material, triggered a demand by the Environmental Working Group for an official enquiry from the National Institute of Environmental Health Sciences (NIEHS), which had funded this work, into Douglass’s behavior. This in turn led to a great deal of press attention to the “scandal” (Begley, WSJ, July 22, 2005). The NIEHS gave the enquiry to Harvard. After a year, Harvard produced a short statement declaring Douglass innocent of unethical behavior, stating that he did not “deliberately” hide Bassin’s findings. Harvard has refused to provide any arguments or explanations supporting this finding despite repeated efforts to get them to do so, from alumni, from citizens and even Congressional representatives.

### **Bassin et al., 2006**

Bassin’s findings were finally published in May 2006 (Bassin et al, 2006). However, the same issue of the journal published a letter from Chester Douglass, downplaying the significance of her findings. It is interesting to contrast Douglass’s “slowness” to warn the public of Bassin’s findings in the four year period between 2001 and 2005, with the speed with which he warned the public that her findings might be “premature” on the very same day that her article appeared in press.

### **The Douglass letter**

In his letter Douglass claimed that Bassin’s findings were based on a subset of a larger cohort, and that the larger cohort did not support her thesis (Douglass & Joshipura, 2006). This was strange because he provided no evidence that her methodology had, at that time, been applied to this larger cohort. Nor is it clear that it has ever been applied to the larger cohort. Douglass further claimed that his larger study (to be co-authored by Robert Hoover who was mentioned above in connection with the NCI review of the SEER cancer registries) would be published in the Summer of 2006.

Douglass had first mentioned the publication date of his study as being the Summer of 2006 in a personal communication to the NRC panel on Jan 3, 2006 (NRC, 2006, p. 329). So it is now over 3 years since this promise was made and the Douglass et al. study has still not been published. Douglass has since retired from his position at Harvard.

### **Douglass’s methodology cannot refute Bassin**

Those who have examined the methodology described by Douglass et al. have indicated that this work would fail to test the central thesis of Bassin’s work (Neurath and Connett, 2008). This is because the biometric of exposure these authors are using - bone fluoride levels found at the time of diagnosis or autopsy - could not be used to ascertain exposure during the years (6- 8) so critical to Bassin’s thesis. This is because fluoride accumulates over time – so a level say at 20 - gives no indication of the level of exposure at 6, 7 or 8.

Moreover, for some bizarre reason the controls being used in the Douglass, Hoover & Whitford study are other bone cancers. Thus, the promised Douglass study would be

invalidated if fluoride caused any of these other bone cancers, like Ewings Sarcoma, which is a distinct possibility.

### **Proponents are using Douglass's letter to negate concern over the Bassin study**

Despite the non-appearance of the promised Douglass et al. study and the limitations in the methodology he has used in terms of refuting Bassin's work, Douglass's letter is being used by fluoridation proponents in several countries, as if it was the final word on the issue. For those who insist on very high standards for the work they accept as evidence, using a "promise" of an unpublished study in a letter to negate Bassin's findings is extraordinary.

This is how the Australian National Health and Medical Research Council (NHMRC) used the Douglass letter in the systematic review they published in 2007.

"The attention of the reader is drawn to a Letter to the Editor that appeared in the same issue of Cancer Causes and Controls by co-investigators on the larger Harvard study (Douglass & Joshipura, 2006). The authors point out that they had not been able to replicate the findings of Bassin and colleagues in the larger study that included prospective cases from the same 11 hospitals. Furthermore, the bone samples that were taken in the broader study corroborate a lack of association between the fluoride content in drinking water and osteosarcoma in the new cases. As Bassin and colleagues acknowledged, the shortcomings of their study mean that their results should be interpreted with caution pending publication of the larger study results" (NHMRC, 2007, p.103)

This is how a local health authority pushing for fluoridation in Southampton, UK used the Douglass letter in their public consultation brochure. You will notice that in this case these authors do not make it clear that reference 13 is not study or "comprehensive review" but a letter promising a study!

"Since 2006, fluoridation opponents have pointed to a study in the United States of America (12) (Reference 12 is the Bassin study, PC) that appears to suggest a possible increase in osteosarcoma (bone cancer) rates in young males – but not females –living in fluoridated areas. However, this was part of a larger study (13) (Reference 13 is the Douglass letter, PC) looking at many more osteosarcoma cases over a longer period of time and including an examination of bone samples. This more detailed and comprehensive review had found no link between water fluoride levels and osteosarcoma. The researchers therefore advised caution in selectively interpreting the results of the smaller study in isolation." (SHA, 2008, pp 18-19)

This is how Dr. Peter Cooney, the Chief Dental Officer of Canada described the Bassin study-Douglass letter in a presentation he gave in Dryden, Ontario on April 1, 2008:

"You are going to hear about osteosarcoma ...some of the studies that did show that there may have been a concern in young males with osteosarcoma have been – in the bigger studies – completely discounted." (Cooney, 2008)

A videotape of Dr. Cooney's whole presentation is available on Google.

The NRC (2006) report was published on March 22, 2006 and thus appeared before the Bassin study was published (May, 2006). However, they were the Fluoride Action Network provided them with a copy of the relevant chapter of her thesis, and one of the NRC panel members reviewed the whole thesis at the Harvard library. The NRC wrote this on Bassin's anticipated paper:

“If this paper provides adequate documentation and analyses or the findings are confirmed by another study, more weight would be given to an assessment of fluoride as human carcinogen.”

### **Postscript**

While the world waits for Douglass's promised paper one is forced to wonder whether a professor in a dental school was the wisest selection to be given such a sensitive study as a possible relationship between fluoridation and osteosarcoma. After all if Douglass were to find such a relationship existed a) he would upset his colleagues who promote fluoridation and b) he would not have made Colgate (a manufacturer of fluoridated dental products ) happy either. Douglass is a consultant for Colgate; in fact, he edits their newsletter. Would this not introduce a serious potential bias to his work?

In the 1991 paper pertaining to this issue (McGuire et al., 1991) for which Douglass was a co-author, it is clear that the authors clearly knew that their findings would threaten the fluoridation program. This paper was published in the Journal of the American Dental Association (JADA) and even though it was a very small preliminary study it was given the full treatment by JADA. It was the cover story for the issue and on the cover appeared the legend all promoters of fluoridation wanted to hear: “Fluoride and Cancer. Study points to protection.” The article was replete with photos of each author and some colorful illustrations.

The McGuire, Douglass and the other authors of this 1991 paper do not hide the fact that they are very concerned about the impacts that a positive finding on a relation with osteosarcoma would have for the fluoridation program, as the following quotes make clear:

“An incorrect inference implicating systemic fluoride carcinogenicity and its removal from our water systems would be detrimental to the oral health of most Americans, particularly those who cannot afford to pay for increasingly expensive restorative dental care” (p.39)

“Because of its strengthening action, fluoride has been widely accepted as the responsible agent for the dramatic declines in the tooth decay rates of U.S. children and adolescents.” ( pp.39-40)

“A disruption in the delivery of fluoride through municipal water systems would increase decay rates over time.” (p.40) (The authors cited the dubious Antigo study to support this claim, PC)

“Linking of fluoride ingestion and cancer initiation could result in a large-scale defluoridation of municipal water systems under the Delaney clause.” (p.40)

The authors concluded based on this small study that there was no relationship between fluoridation and osteosarcoma, and even hypothesized that:

“fluoridation at recommended levels may provide a **protective** effect against the formation of osteosarcoma” (p.44) (my emphasis, PC)

Which allowed Douglass and his co-authors to reach the final conclusion they clearly wanted out of this study:

“Given present knowledge, every effort should be made to continue the practice of fluoridating community water supplies.” (p. 45)

Such concerns about the fate of the fluoridation program are in sharp contrast to the very limited concerns the authors express about the fate of the young men who succumb to osteosarcoma. This is a frequently a fatal cancer and, at the very least, results in a loss of a limb. By any other standards this would be a very heavy price to pay for the saving of a modest amount of tooth decay.

Other than attempting to minimize the previous evidence that a relationship between fluoride exposure and osteosarcoma might exist, and discussing other causes of the disease, the only thing Douglass and his co-authors had to say about this possible disastrous outcome of drinking fluoridated water was:

“Osteosarcoma is a rare and painful primary malignant bone tumor most commonly occurring in children and young adults. Data indicate that tumors of the bones and joints occur in less than one person in 100,000.” (p.39)

In the 18 years since this McGuire et al. paper was published, Douglass has received over a million dollars in funding from the NIH. This massive funding began in 1992 after Douglass’s concerns that a positive finding on osteosarcoma would sabotage the fluoridation program. Apart from one abstract, and the letter sent to the journal which published Bassin’s study, Douglass has never published the results of his work. However, his promises of publications to come continue to keep the lid on this explosive issue.

## References

Commentary on Bassin E.B. (2001). Association Between Fluoride in Drinking Water During Growth and Development and the Incidence of Osteosarcoma for Children and Adolescents. Doctoral Thesis, Harvard School of Dental Medicine.

Bassin E.B., Mittleman M.A., Wypij D., Joshipura K., Douglass C.W. (2004). Problems in exposure assessment of fluoride in drinking water. *Journal of Public Health Dentistry* 64:45-9.

Bucher J. (1990). Peer Review of Draft Technical Report of Long-Term Toxicology and Carcinogenesis Studies and Toxicity Study, Sodium Fluoride; Research Triangle Park, North Carolina, Thursday, April 26, 1990. p. 30-31.

Bucher J.R., Heitmancik M.R., Toft J., Persing R.L. Eustis S.L. Haseman J.K. (1991). Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride. *International Journal of Cancer* 48(5):733-7.

Caspary WJ, et al. (1987). Mutagenic activity of fluorides in mouse lymphoma cells. *Mutation Research* 187:165-80.

Cohn P.D. (1992). A Brief Report On The Association Of Drinking Water Fluoridation And The Incidence of Osteosarcoma Among Young Males. New Jersey Department of Health Environ. Health Service.

Connett,P , Neurath,C and Connett,M. Revisiting the Fluoride-Osteosarcoma connection in the context of Elise Bassin's findings: Part I Submitted to the NRC review panel on the Toxicology of Fluoride in Water March 2, 2005  
<http://www.fluoridealert.org/health/cancer/fan-nrc.part1.pdf>

Connett, P, Neurath, C and Connett, M. (2005) Revisiting the Fluoride-Osteosarcoma connection in the context of Elise Bassin's findings: Part II Submitted to the NRC review panel on the Toxicology of Fluoride in Water March 21, 2005 revised April 8, 2005  
<http://www.fluoridealert.org/health/cancer/fan-nrc.part2.pdf>

Douglass CW & Joshipura K (2006). Caution needed in fluoride and osteosarcoma study. *Cancer Causes & Control*, 17: 481-2.

Food & Drug Administration (FDA). (1990). Dose determination and carcinogenicity studies of sodium fluoride in Crl:CD-1 Mice and Crl:CD (Sprague Dawley)BR Rats. In: Department of Health & Human Services. (U.S. DHHS) (1991). Review of Fluoride: Benefits and Risks. Report of the Ad Hoc Committee on Fluoride, Committee to Coordinate Environmental Health and Related Programs. Department of Health and Human Services, USA. pp. D1-D7.

Freni S.C., Gaylor, D.W. (1992). International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer* 70:611-8.

Gelberg K.H. (1994). Case-control study of osteosarcoma. Doctoral Thesis, Yale University.

Gelberg K.H., Fitzgerald E.F., Hwang S., Dubrow R. (1995). Fluoride exposure and childhood osteosarcoma: a case-control study. *American Journal of Public Health* 85:1678-83.

Hoover R.N., Devesa S.S., Cantor K.P., Lubin J.H., Fraumeni J.F. (1991). Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute. In: Review of Fluoride: Benefits and Risks Report of the Ad Hoc Committee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs US Public Health Service. Appendix E and Appendix F.

Hrudey S.E., Soskolne C.L., Berkel J., Fincham S. (1990). Drinking water fluoridation and osteosarcoma. *Canadian Journal of Public Health* 81(6):415-6.

Joseph S, Gadhia PK. (2000). Sister chromatid exchange frequency and chromosome aberrations in residents of fluoride endemic regions of South Gujarat. *Fluoride* 33: 154-158.

Kishi K, Ishida T. (1993). Clastogenic activity of sodium fluoride in great ape cells. *Mutation Research* 301:183-8.

Lee J.R. (1993). Fluoridation and Bone Cancer. *Fluoride* 26:79-82.

Lee J.R. (1996). Fluoride exposure and childhood osteosarcoma. A case control study. *Fluoride* 29:237-240.

Mahoney M.C., Nasca P.C., Burnett W.S., Meius J.M. (1991). Bone cancer incidence rates in New York State: time trends and fluoridated drinking water. *American Journal of Public Health* 81:475-9.

Marcus W. (1990). Memorandum from Dr. William Marcus, to Alan B. Hais, Acting Director Criteria & Standards Division ODW, US EPA. May 1, 1990.  
<http://www.fluoridealert.org/marcus.htm>

McGuire S.M., Vanable E.D., McGuire M.H., Buckwalter J.A., Douglass C.W. (1991). Is there a link between fluoridated water and osteosarcoma? *Journal of the American Dental Association* 122:38-45.

McGuire S.M., Douglass C.W., Joshi A., Hunter D., DaSilva J. (1995). Fluoride exposure and osteosarcoma. [Abstract] *J Dent Res* 74:98.

Meng 1997

Mihashi M., Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. *Mutation Research* 368:7-13.

Moss M.E., Kanarek M.S., Anderson H.A., Hanrahan L.P., Remington P.L. (1995). Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989. *Archives of Environmental Health* 50:235-41.

National Academy of Sciences (1977). *Drinking Water and Health*. National Academy Press, Washington, DC. pp. 388-389.

National Toxicology Program [NTP] (1990). *Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3f1 Mice*. Technical report Series No. 393. NIH Publ. No 91-2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

National Research Council (1993). *Health effects of ingested fluoride*. Report of the Subcommittee on Health Effects of Ingested Fluoride. National Academy Press, Washington, DC.

Operskalski E.A., et al. (1987). A case-control study of osteosarcoma in young persons. *American Journal of Epidemiology* 126:118-26.

Schlesinger, E.R., Overton, D.E., Chase, H.C., and Cantwell, K.T. (1956). Newburgh Kingston Caries-Fluorine Study XIII. Pediatric Findings After ten Years. *Journal of the American Dental Association*, 52:297-306.

Sheth FJ, et al. (1994). Sister chromatid exchanges: A study in fluorotic individuals of North Gujarat. *Fluoride* 27: 215-219.

Takahashi K., Akiniwa K., Narita K. (2001). Regression analysis of cancer incidence rates and water fluoride in the U.S.A. based on IACR/IARC (WHO) data (1978-1992). International Agency for Research on Cancer. *Journal of Epidemiology* 11(4):170-9.

Tsutsui T, Suzuki N, Ohmori M, Maizumi H. (1984). Cytotoxicity, chromosome aberrations and unscheduled DNA synthesis in cultured human diploid fibroblasts induced by sodium fluoride. *Mutation Research* 139:193-8.

World Health Organization (2002). *Environmental Health Criteria 227: FLUORIDES*. World Health Organization, Geneva.

Wu DQ, Wu Y. (1995). Micronucleus and sister chromatid exchange frequency in endemic fluorosis. *Fluoride* 28: 125-127.

Yiamouyiannis J. (1993). Fluoridation and cancer: The biology and epidemiology of bone and oral cancer related to fluoridation. *Fluoride* 26:83-96