



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

**MEMORANDUM**

**One of Four**

DATE: May 1, 1990

OFFICE OF  
WATER

SUBJECT: Fluoride Conference to Review the NTP Draft Fluoride Report

FROM: Wm L. Marcus, Ph.D., Senior Science Advisor  
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TO: Alan B. Hais, Acting Director  
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The conference was held in RTP at the NIEHS headquarters on April 26, 1990. The subject of the conference was a peer review of the NTP draft report on the toxicology and carcinogenesis studies of Sodium Fluoride in F344/N Rats and B6C3F<sub>1</sub> Mice (Drinking Water Studies) NTP Report Number 393. Dr. Robert Scala was to chair this meeting but was unable to attend because of ill health. Dr. Michael Gallo was appointed acting Chairperson. One of the attenders seated with the panel members was David Rall, Ph.D., M.D., Director of NIEHS. Dr. Rall took an extremely active interest in the proceedings and remained seated for the entire proceedings with only two minor interruptions.

The most disturbing part of the report was the continual reference to the historical controls as having the same or higher cancers as the test groups. On pages 89 - 90 of the report starting with the last paragraph the authors state the following:

*An important consideration which limits the usefulness of the historical control data base in the interpretation of the current studies is that the diet used in all other NTP studies had not been closely controlled or monitored for fluoride content. Fluoride concentrations in typical batches of NIH-07 diet range between 28 and 47 ppm (.7 and 1.2 mg/kg/day) (Rao and Knapka<sup>1</sup>, 1987). Assuming a maximum bioavailability of 60% (Tests show 64% absorption page I-18), the historical database animals actually constitute a group receiving sufficient fluoride sufficient to place them between the low- and mid-concentration group in the current (the studies reviewed at RTP at this conference). The fact that this fluoride is available for absorption from the standard diet is supported by the levels of fluoride found in the bones of animals maintained on this diet in the six months studies (Appendix 1). (The levels in the bones of the rats on the standard NIH chow was ten [10] times the levels of those*

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<sup>1</sup>Roa, G.N., and Knapka, J.J. 1987. Contaminant and nutrient concentrations of natural ingredient rat and mouse diet used in chemical toxicology studies. *Fundam. Appl. toxicol.* 9, 329-338.

fed the semisynthetic diet and deionized water, 0.922 vs 0.0901). *If the fluoride in fact influencing the "spontaneous" or background incidence of osteosarcomas in male rats, comparisons with those in the historical database maybe misleading. This forces an even greater reliance on the within-study comparisons, i.e., the incidences of the dosed groups compared with the concurrent control, in the interpretation of the results of the sodium fluoride studies.*

When I plotted a bar graph of osteosarcoma in male rats and placed the historical controls on the graph 0.6% is just where expected. This helps demonstrate a relationship between osteosarcoma and fluoride. The purpose of such graphs is to predict occurrence. Since the historical controls comprise some 6,000 animals, this data point is extremely significant compared to the other three. Osteosarcoma is an extremely rare animal tumor and may be the result of the variable high fluoride content in the feed. In order to demonstrate this, all that need be done is require that the fluoride content of animal chow be lowered dramatically and that fluoride be removed from the water given to the animals under study.

The dose of fluoride to which the concurrent controls were exposed is 0.2 mg/kg/day. A 70 kg man who drinks 2 liters daily is exposed to 0.03 mg/kg/day. The "control" animals were exposed to an amount of fluoride six to seven (6-7 X) greater. Lois Gold, Ph.D. of the review panel concluded that, "this group of animals therefore, can hardly be termed a control group. It can best be described as a lowest dosed group." This is an important consideration because as the document reports on page 9, the levels of fluoride in bone are linearly dependent upon dose and length of exposure ("depend upon total intake") in people. The level of fluoride in ashed samples of bone of 20-30 year old people is 200 - 800 mg/kg compared to 70 to 80 year old people of 1,000 - 2,500 mg/kg. In the document, the authors cited Zipkin<sup>2</sup> who reported on bone fluoride concentrations in four groups of individuals with average ages of 56 to 76 who lived in areas with fluoride concentrations in drinking water of 0.1, 1, 2.6, or 4 ppm. The relationship to bone fluoride concentrations and water fluoride content was linear; bone fluoride ranged from about 800 to 7,000 ppm ash with increasing water fluoride."

In the animal studies the levels of fluoride (Appendix I) found in the bones of the animals were the same as or lower than those found in people. The highest dosed level of rats had lower levels of fluoride in their bones (5,470 ppm) compared to people (7,000 ppm) at the MCL of 4 ppm. This can be interpreted as people who ingest drinking water at the MCL have 1.3 times more fluoride in their bones than male rats who get osteosarcoma. This is the first time in my memory that animals have lower

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<sup>2</sup>Zipkin, L., McClure, F.J., Leone, N.C., and Lee, W.A. 1958. Fluoride deposition in human bones after prolonged ingestion of fluoride in drinking water. *Public Health Rep.* 73, 732-740.

concentrations of the carcinogen at the sight of adverse effect than do humans. An important toxicologic consideration is that a toxic substance stores at the same place it exerts its toxic activity. This is true of benzene and now for fluoride. Fluoride however, is at twice the concentration in human bones compared to benzene which is 10 to 100 greater in animal marrow. This portends a very serious problem. One would expect to be able to discern a carcinogenic effect in the exposed population when compared to the unexposed population especially if data exist on the populations before fluoridation.

Yiamouyiannis and Burk published epidemiology studies that have since been revised twice<sup>3</sup>, by Burk (former head of the Cytochemistry section at NIH). In these extensively peer reviewed papers, the authors found that about 10,000 deaths a year are attributable to fluoride water treatment. The U.S. Public Health Service (U.S.PHS) criticized the original studies by erroneously asserting that the results reported by the authors were a result of changes in the age, race and sex composition of the sample. The U.S.PHS made mathematical errors and did not include 90% of the data. The U.S.PHS method of analysis when applied to the database, confirmed that 10,000 excess cancer deaths yearly were linked to fluoridation of water supplies. This evidence has been tested most recently in the Pennsylvania Courts and found scientifically sound after careful scrutiny.

There were three different short term *in vitro* tests performed on fluoride and all these tests proved fluoride to be mutagenic. An Ames test was performed and reported to be negative. Bruce Ames, in a letter to Arthur Upton introduced in the Congressional Record, stated that his test system was inappropriate for fluoride testing based on a number of technical considerations. EPA's own guidelines require that *in vitro* tests be taken into consideration when found positive. In this case, the mutagenicity of fluoride supports the conclusion that fluoride is a probable human carcinogen.

Melvin Reuber, M.D., a board certified pathologist and former consultant to EPA and part time EPA employee, reviewed some of pathology slides and the Battelle report. Dr. Reuber has had his pathologic diagnoses questioned several times in the past. When an independent board together with Dr. Reuber went over the slides his opinion was always upheld. He first published the work that identified hepatocholangiocarcinoma as a pathologic entity. The report changed Battelle's board certified veterinary pathologists diagnoses from hepatocholangiocarcinoma to hepatoblastoma and finally to hepatocarcinoma. Dr. Reuber reviewed the pathology slides and stated that these lesions are indeed hepatocholangiocarcinoma. Because Dr. Reuber first identified and

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<sup>3</sup>Graham, J.R., Burk, D., and Morin, P. 1987. A current restatement and continuing reappraisal concerning demographic variables in American time-trend studies on water fluoridation and human cancer. *Proc Pennsylvania Academy of Sci.* 61:138-146.

