UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON. D.C. 20460

MEMORANDUM **One of Four**

Office of

DATE: May 1. 1990 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, 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 attendees 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 concentration in typical batches of NIH-07 diet range between 28 and 47 ppm (*. 7 and 1.2 mg/kg/day)*(Rao and Knapka[1] 1987). Assuming a maximum bioavailability of 60% (Tests show 64% absorption page 1-18), 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 for six month studies (Appendix 1).* (The levels in the bones of the rats on the standard NIH chow was ten [10] times the level of those

[1]Roa, G.N., and Knappa, 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.

{Summary and Glossary Attached}

> 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 incidence 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[2] *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 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

[2]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 it 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[3], 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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[3]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.

published his findings on this tumor, I trust his opinion in this matter. These tumors are extremely rare. Dr. Reuber's diagnoses would make the liver cancers significant because of their rarity. This changes the equivocal findings of the board to at least some evidence or clear evidence of carcinogenicity. In addition, the oral changes in the report were down-graded from dysplasia and metaplasia to degeneration. Dr. Reuber said that this change should also be reviewed. The report also down-graded adrenal pheochromocytomas and tumor to hyperplasia. This needs to be reviewed by an independent board. The other liver carcinomas were down-graded to foci by artificially defining a need for 75% compression in the tumor before it was no longer a foci. Using this changed definition carcinomas were down-graded to adenomas and adenomas downgraded to eosinophilic foci. In almost all instances, the Battelle board certified pathologists' findings were down-graded. It is my suggestion that a board independent of NIEHS should be assembled by ODW consisting of human pathologists (for their experience in diagnosing osteosarcoma), the Battelle pathologist (to defend his original diagnoses), Dr. Melvin Reuber. Dr. Thomas Squires and two other well known independent board-certified animal pathologists. The charge to this board is to meet as a body, review the slides, agree on a pathologic diagnoses and prepare a report to be submitted to ODW for incorporation in our docket for the fluoride regulation.

The report talks about the efficacy of fluoride and tooth decay. Since the studies were performed to determine the carcinogenicity of fluoride this should not have been addressed. There appear to be at least four different publications from the U.S., Canada, and New Zealand that have reported similar or lower tooth decay rates in nonfluoridated areas as compared to fluoridated areas[4,5,6,7]. Therefore, the entire question of the efficacy of fluoridation based on extensive and multiple studies has been called into question. Our job is to set safe levels for fluoride in drinking water based on the scientific evidence.

The problem with this meeting was the inability of independent reviewers to get to see the slides prior to the meeting. We must perform our own scientific review of the slides and write our conclusions for use in the development of the revised fluoride regulation.

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[4]Colquhoun, J. 1987. *Comm. Health Studies.* 11:85.

[s]Gray, S. 1987. *J. Canadian Dental Assoc.* 53:763.

[6]Hildebolt, C.F. et al. 1989. *Amer J. Physiol. Anthropol.* 78:79-92.

[7]Diesendorf, M. 1986. Nature. 322:125.

SUMMARY AND GLOSSARY

The attached May Day 1990 memo is an exact replica of the original which was the key piece of evidence in Dr. Marcus' successful whistle blowers lawsuit. In this document Dr. Marcus accuses the U.S. Public Health Service of scientific fraud in the alteration of the NTP (National Toxicological Program) finding of fluoride carcinogenicity. The pathologists who have examined the liver tumors pathology slides agree that they are in fact hepatocholangiocarcinomas.

No consideration was given to the three positive in-vitro test for mutagenicity. Dr. Marcus stated that the use of controls from other studies was clearly inappropriate. Those animals from unrelated studies were given very high fluoride food. The daily dose of fluoride placed them in the mid dose group. Their exposure to excessive fluoride was confirmed by bone fluoride levels more than 10 times higher than the low dose controls.

Therefore, fluoride is a carcinogen. The U.S. PHS service following a 50 year program of fraud and cover-up of fluoride toxicity changed these critical cancer findings. The real reason for the PHS demand for nationwide fluoridation can be found on the web pages article by Joel Griffith posted on `http://www.inter-view.net/~sherrell/bomb.htm`

All in all, the facts speak for themselves. There is now ample evidence that fluoride in drinking water causes an increase in cancers. It is time to **stop drinking water fluoridation** for the alleged purpose of tooth decay prevention. See Fluoride Issues at `http://www.sonic.net/~kryptox/fluoride.htm`

Posted on Web page of the Preventive Dental Health Association;
`http://emporium.turnpike.net/P/PDHA/fluoride/blunder1.htm`

GLOSSARY of Abbreviations

Cytochemistry	Cell chemistry
EPA	Environmental Protection Agency
MCL	Maximum Contaminant Level
mg/kg/day	Milligrams per kilogram per day
NIEHS	National Institute of Environmental Health Science
NIH-07	National Institute of Health Standard Rat/mouse Food
NIH	National Institute of Health
NTP	National Toxicological Program
ODW	Office of Drinking Water
PPM	Parts per million
RTP	Research Triangle Park
U.S.. PHS	United States Public Health Service

7344/N	Rats breed ID number
B6C3F	Mice breed ID number