



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
Criteria & Standards Division, ODW (WH-550D)

TO: Alan B. Hais, Acting Director
Criteria & Standards Division, ODW (WH-550D)

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 B6C3F₁ 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 Knapka¹, 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

¹Roa, 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 Zipkin² 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

²Zipkin, 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 twice³, 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

³Graham, 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 finding 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 tumors 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 down-graded 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 non-fluoridated 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.

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

⁵Gray, S. 1987. *J. Canadian Dental Assoc.* 53:763.

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

⁷Diesendorf, M. 1986. *Nature*. 322:125.



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

OFFICE OF
WATER

MEMORANDUM

DATE: May 4, 1998

SUBJECT: A 10% Decrement in I.Q. in Chinese Children as a Result of Fluoride

FROM: William L. Marcus, Ph.D., D.A.B.T., Senior Science Advisor
Office of Science and Technology, 4301

TO : James A. Hanlon, Deputy Director
Office of Science and Technology, 4301

Keeping abreast of the literature, I came across and perused two papers from China^{1,2} that report the effect of fluoride on the intelligence of children in the provinces of China detailed below. The authors determined that fluoride caused a 10% decrement in I.Q. Lead caused approximately 1% decrement in I.Q. was responsible for the current lead regulation and the prohibition of adding lead [tetra ethyl (methyl)lead] to gasoline.

The Chinese using their own I.Q. tests measured more than 900 children in Guizhou Province between the ages of 8 and 13. The Dean's method of dental fluorosis and urinary fluoride concentrations was used by the Chinese to divide the cohort of children into geographical areas of fluorosis: slight fluorosis, medium fluorosis, and severe fluorosis. The cohort of children was also divided by I.Q. into <70 low; 70-79 borderline; 80-89 medium; 110-119 upper medium; 120-129 excellent; 129 special excellence. The data shows that there is on average a 10 point decrease in I.Q. of children between the non-fluorosis area and the medium or severe fluorosis areas. The authors state, "that the central nervous systems of children ... are adversely affected by fluoride." "Because no correlation was found between age and I.Q. for children in the medium and severe fluorosis areas, it appears that the influence of a high

¹Zhao, L.B., Liang, H.H., Zhang, D.N. and Wu, X.R. 1996. Effect of a High Fluoride Water Supply on Children's Intelligence. Fluoride. 29(4) 190-192. Lu-Liang Public Health Bureau, and Epidemic Station Shanxi.

²Li, X.S., Zhi, J.L. and Gao, R.O. 1995. Effect of Fluoride Exposure on Intelligence in Children. Fluoride 28(4): 189-192. Guizhou Provincial Sanitary and Anti-Epidemic Station, Guiyang City, Anshun Prefecture Sanitary and Anti-Epidemic Station and Zhijin County Sanitary and Anti-Epidemic Station.

fluoride environment on the development of intelligence may occur early in development such as during stages of embryonic life or infancy when the differentiation of growth of the nervous system is most rapid (ibid.)."

The Chinese obtained "human embryonic brain tissue from termination of pregnancy operations (ibid.)" that showed the differentiation of brain nerve cells was poor, and brain development was delayed.

The paper from Lu-Liang Province compared a village that had high-fluoride drinking water (4.12 mg/l) where 86% of the population have dental fluorosis, and 9% have bone fluorosis to a village in which only 14% of the population have dental fluorosis with no bone fluorosis. "The results of this study indicate that intake of high-fluoride drinking water from before birth has a significant deleterious influence on children's I.Q. in one of two similar villages. No real difference was found for gender. .. The number of children with I.Q. scores of 69 or below was 6 times that in the healthier low-fluoride village." There was a significantly lower number of children with I.Q. scores that are 110 or higher (45 vs 70) in the high fluoride village. When the adults were screened it showed that the I.Q. scores did not improve with age.

I want to work with the Agency through the established chain of command to insure that the scientific issues are addressed in a professional and proper manner. Given my expertise on the effect of lead on the development of children's I.Q., my position as Senior Science Advisor, and my position description, I should lead a small group of scientists in a preliminary inquiry to determine if this research reaches a potential threshold of scientific validity. The validity and the methods used to collect and analyze the data first have to be carefully examined before the conclusions of these two papers can be tested.

If the preliminary review confirms that the data, methods and analyses as presented have merit I will request immediate permission to go to China along with a small committee of appropriately qualified scientists to interview and review with the authors their research and subsequent findings.



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

OFFICE OF
WATER

MEMORANDUM

DATE: May 22, 1998

SUBJECT: Facsimiles of Requested Fluoride and Related Papers

FROM: William L. Marcus, Ph.D., D.A.B.T., Senior Science Advisor
Office of Science and Technology, 4301

TO: Arnold Kuzmack, Ph.D., Senior Advisor
Office of Science and Technology, 4301

Some recently published research papers on fluoride
Attached are the facsimiles of the papers you requested that I brought to the May 6 meeting.

- The paper, coauthored by EPA scientist Karl F. Jensen, describes alterations in the nervous system as a result of administration of fluoro-aluminum complex (AlF_3) or an equivalent amount of fluoride (F). The authors noted that ingestion of fluoride or aluminum fluoride complex (AlF_3) produced, "striking parallels between Al-induced alterations in the cerebro-vasculature those associated with Alzheimer's disease (AD) and other forms of dementia." Both *free flowing table salt and ground pepper* use aluminum chloride to prevent clumping due to ambient moisture. The fluoride compound commonly added to drinking water systems also contains aluminum.
- The papers from China report that fluoride caused a 10% decrement in I.Q. in children. Lead which causes approximately a 1% decrement in I.Q. was responsible for the current lead regulation and the prohibition of adding lead [tetra ethyl (methyl)lead] to gasoline.
- The Chinese obtained "human embryonic brain tissue from termination of pregnancy operations." that showed the differentiation of brain nerve cells was poor, and brain development was delayed.
- Dr. Mullinex showed that there are dose dependent increases in brain fluoride up to 7.3 times higher in males that correlate with cognitive deficits. Experience with lead and methylmercury show that *cognitive deficits occur in children at much lower exposure levels* than can be reliably measured in animals. The blood and/or tissue levels of exposed

infants or children that correlate with cognitive deficits are at least one or more often two magnitudes lower than the animal model.

- Appendix C of the Schatz paper is a critical analysis of Report 122 by the British Department of Public Health and Social Security in London, "Special Committee on Research into Fluoridation report. "Figure 1(derived from Table 7 of Report 122) conclusively proves that fluoride does *not* reduce the amount or rate of tooth decay." The figure shows that there was no difference between the slopes (rate of decayed, missing and filled teeth versus age) of the nonfluoridated and fluoridated children (8 to 14+ years of age). The onset of dental caries was delayed about 1.2 years.

In the Jensen paper, the simple addition of sodium fluoride increased aluminum (Al) brain levels two fold when compared to controls. Similarly AlF₃ produced brain Al levels more than two fold greater than controls. The paper concludes that fluoride contributes to higher levels of aluminum in the brain in animals which received AlF₃, as well as those who received just F.

Those animals with higher aluminum levels had in the left hemisphere of their brains the following abnormalities:

- Chromatin clumping (in the cell nucleus)
- Enhanced protein staining
- Pyknosis
- Vacuolization
- And the presence of ghost like cells

The kidney Al levels were twice control in the NaF group and at least four times that of controls. Twenty-seven adult Long-Evans rats were divided into three groups of nine rats. One group of nine imbibed either double distilled deionized drinking water (ddw), a second group of nine imbibed 0.5 ppm of AlF₃ dissolved in ddw, and the third group 2.1 ppm of NaF. The molar amount of available F in the drinking water was identical in both treatment groups.

Brain Research Journal article:

Varner, J.A., Jensen, K.F.¹, Horvath, W. and R.L. Isaacson. 1998. Chronic Administration of Aluminum-fluoride or Sodium-fluoride to Rats in Drinking Water: Alterations in Neuronal and Cerebrovascular Integrity. *Brain Research* 784:284-298.

The two Chinese studies:

Zhao, L.B., Liang, H.H., Zhang, D.N. and Wu, X.R. 1996. Effect of a High Fluoride Water Supply on Children's Intelligence. *Fluoride*. 29(4) 190-192. Lu-Liang Public Health Bureau, and Epidemic Station Shanxi.

¹Neurotoxicology Division, NHEERL, EPA, Research Triangle Park, NC, USA

Li, X.S., Zhi, J.L. and Gao, R.O. 1995. Effect of Fluoride Exposure on Intelligence in Children. *Fluoride* 28(4): 189-192. Guizhou Provincial Sanitary and Anti-Epidemic Station, Guiyang City, Anshun Prefecture Sanitary and Anti-Epidemic Station and Zhijin County Sanitary and Anti-Epidemic Station.

Dr. Mullinix showed that there are dose dependent increases in brain fluoride levels of 5 to 6 month old rats exposed for twenty weeks beginning at 21 days of age. The brain fluoride levels were up to 5.4 or 7.3 times higher than controls in female or male rats respectively. There are cognitive deficits in rats exposed as weanlings or adults. Prenatal exposure induces behavioral changes such as those seen in drug induced hyperactivity.

Experience with lead and methylmercury show that cognitive deficits occur in children at much lower exposure levels than can be reliably measured in animals. The blood and/or tissue levels of exposed infants or children that correlate with cognitive deficits are also one or two magnitudes lower.

Mullenix, P.J., Denbesten, P.K., Schunoir, A. and W.J. Kernan. 1995. Neurotoxicity of Sodium Fluoride in Rats. *Neurotoxicology and Teratology*. 17(2):169-177.

The Spittle review paper examines most of the well known high level fluoride effects. Included however is a description of psychological effects that occurred in people ingesting 1.5 ppm during a double blind experiment. Some of the individuals experienced migraine headaches, visual disturbances and depression². A causal relationship between the initiation of HF emissions from a new factory showed both time, meteorological and physical distance to be related to the chronological onset and severity of the following symptomology: generalized progressive fatigue (most often reported), decline in mental acuity, increased forgetfulness, inability to coordinate thought, and a reduced ability to write; 15 cases of parathesias, 14 cases of cephalgia, 7 cases of vertigo, 6 cases of impaired vision and 6 cases of scotomata.

Spittle, B. Psychopharmacology of Fluoride: a review. 1994. *Int. Clin. Pyschopharmacol.* 9:79-82.

Foulkes, R.G. The Fluoride Connection. 1996. *Fluoride*. 29(4):230-236.

This paper further discusses in detail the Chinese papers. There is substantial editorializing and speculation. However Dr. Foulkes put the Chinese data in a graphic format. This analyses demonstrates unequivocally: a flattening of the bell curve for I.Q., the significant lowering of children's I.Q. in the highly fluoridated areas (figures 2 and 4) based on the percentage of the population at a given age with a specific I.Q.

Shatz, A. 1996. Low level fluoridation and low level radiation. Two cases of misconduct in science.

²Grimbergen, G.W. 1974. A Double Blind Test for determination of Intolerance to Fluoridated Water. *Fluoride*. 7:146-152.



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

OFFICE OF
WATER

May 25, 1999

MEMORANDUM

DATE: May 25, 1999

SUBJECT: Fluoride Update on Adverse Effects on Intellect

FROM: William L. Marcus, Ph.D., D.A.B.T., Senior Science Advisor
Office of Science and Technology, 4301

TO: Tudor Davies, Office Director
Office of Science and Technology, 4301

During the past year I have written three memoranda to the Office Of Science and Technology concerning emerging science literature reporting a 10% decrease in I.Q. caused by drinking water exposure to fluoride. I do not know if my efforts were lost in transit for I have not received any indication or acknowledgment of the new information. I have therefore attached copies for your review.¹

In August 1998 my concern reached a level of intensity such that I thought that review by an independent working group would be needed to provide unbiased judgement and direction. A memorandum was written to this effect. It too has gone unacknowledged. A copy is enclosed.²

The third memorandum dealt with the potential direction which our programs might consider in response to the fluoride data. Once again it appears to have been lost.³

Time has only heightened my concern. Drinking water supplies are being fluoridated using fluorosilicic acid. Now there have been additional developments in this field of knowledge.

A scholarly work published by the Ohio Experiment Station Bulletin (no. 558) pages 3-77, in 1935, established that fluorosilicic acid is absorbed by chickens, pigs and rats at three times or more than the rate of other fluoride containing compounds. The paper is entitled, Fluorine in Animal Nutrition was written by Kick CH., Bethke RM., Edington B H, Wilder OHM, Record PR, Wilder W, Hill TJ and Chase SW.

It would appear highly likely that humans also absorb at least three times more fluoride from fluorosilicic acid than from other forms of fluoride as well. Thus allowable exposure levels might yield intakes 3 times higher than assumed in the regulatory process.

Our regulations are based on sodium fluoride addition. The switch to fluorosilicic acid means that the 1 ppm level is in effect the same as a three or more ppm.

Dr. Phyllis Mullinex wrote a letter, on May 5, 1999 to BSA Environmental Services hired by Headquarters, U.S. Army Medical and Material Research Command to look in to the potential problems in fluoridation. Her letter (attached) contains significant new information and associations concerning the adverse effects of fluoride on intellect.

She performed a literature review that "assembled case reports spanning 60 years on neurological effects of in humans exposed to fluoride. A common theme in these reports was that fluoride exposure impaired memory and concentration and it caused lethargy, headache, depression, and confusion. The depression is not something to ignore because suicide occurs more frequently than expected in populations of fluoride workers."

A clinical study of children treated for leukemia... found that the fluorinated steroid (dexamethasone) was more detrimental to IQ than its non-fluorinated steroid counterpart (prednisolone). The study in children showed there were greater deficits " in reading comprehension, arithmetic calculation and short term working memory."

"There is a recent study funded by EPA (Coplan and Masters) which reports that silicofluorides in fluoridated drinking water increase levels of lead in children's blood, a risk factor that predicts higher crime rates, attention deficit disorder and learning disabilities ."

These findings correlate with the animals studies carried out by Dr. P.J. Mullinex which showed that:

- brain function was vulnerable to fluoride in rats;
- the effects on behavior depended on age at time of exposure;
- fluoride accumulated in brain tissue;
- exposed adults displayed behavior-specific changes typical of cognitive deficits;
- prenatally exposed rats had behaviors typical of hyperactivity.

I strongly recommend that it would be prudent for the Office carry out a plan similar to that outlined in my memorandum of August 11, 1998, Establishment of Fluoride Working Group.

I wrote three memoranda concerning a potential 10% decrease in I.Q. caused by fluoride nearly one year ago. (Attached):

1. A 10% Decrement in I.Q. in Chinese Children as a Result of Fluoride, May 4, 1998;
2. Establishment of Fluoride Working Group, August 11, 1998;
3. Programmatic Response to Emerging Toxicology Data-Fluoride, August 31, 1998.

