EPA FILE

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Bellack.

National Institutes of Health
Bethesda, Maryland 20205

May 26, 1983

Dear Committee Member:

I am sending you a first draft which summarizes the discussions of the committee in regard to the nondental toxicity of fluoride in drinking water. This draft follows the transcript, and it includes some background material which I think will be helpful to interested parties who will no doubt carefully review the committee's recommendations. In a final copy, I will insert the appropriate references.

I am leaving the Washington, DC, area on June 12. It is essential that I receive your comments as quickly as possible so that they can be incorporated into a final statement. The transcript of the meeting filled two volumes and totaled more than 400 pages. I have not copied it, but if anyone is interested, I will be happy to make a copy and send it.

You all probably are aware of the interest our meeting generated, in part because the American Dental Association cited it in a recent newsletter sent to a very large audience.

Please give this your prompt attention and do not hesitate to call if you feel it necessary. All comment is welcomed!

Again, I appreciate your assistance and participation in completing the report of the committee to the Surgeon General.

Sincerely yours,

Jay R. Shapiro, M.D.
Deputy Director
The Clinical Center

Enclosure

Final comments 1.0

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DRAFT

In February 1982, the Environmental Protection Agency (EPA), in the process of re-examining the relationship of fluoride in drinking water to dental fluorosis, requested a review of the scientific basis of the health effects of fluorosis by the Public Health Service (PHS).

An ad hoc committee on dental fluorosis subsequently reported (March 1982) that "twice optimum (1.4-2.4 mg/l) is a conservative PHS standard for a maximum recommended concentration in natural drinking water supplies." They concluded that "two times the optimum concentration be used as a guide as to which communities should consider fluoride removal since there is evidence that dental health benefits do not significantly improve above that point." Following this report the Surgeon General (1982) stated that a) "No sound evidence exists which shows that drinking water with the various concentrations of fluoride found naturally in public drinking water has any adverse effect on general health, and b) that "to minimize the occurrence of undesirable cosmetic effects it is prudent to maintain the upper limit of fluoride in drinking water at two times the recommended optimum concentration."

In February 1983, EPA requested that the PHS conduct a medical review to determine the level at which adverse health effects may result as a consequence of fluoride

in natural drinking water supplies and the margin of safety which would be appropriate. This review was to be directed at general health effects of fluoride, to determine if the safety margin falls within the concentration of fluoride found in some U.S. drinking water supplies.

Specifically, four issues identified by the EPA were:

1. Could fluoride have any adverse or potential effect on health?
2. Do the levels of fluoride in drinking water meet the criteria of the Safe Drinking Water Act, e.g. "have any adverse effect from or a stipulated on the health of persons" - thus warranting continuation of a primary drinking water regulation for fluoride?
3. What would be the "highest no observed adverse effect exposure level" and/or the "lowest observed adverse effect level?"
4. In consideration of the 1981 petition by the state of South Carolina to remove fluoride from primary drinking water regulations, should 1) a secondary regulation or 2) special monitoring or notification requirements for fluoride in drinking water be formulated by the agency?

The current fluoride maximum contaminant level of 1.4-2.4 mg/l was established in 1975 as an interim primary regulation. EPA at that time considered the potential health effects of fluoride above two times the optimum to be adverse health effects. These included severe dental fluorosis, osteosclerosis (at 8 mg/l or above), and crippling fluorosis (at 20 mg/l or above) as adverse

In March 1983, at the direction of the Surgeon General, an ad hoc committee was organized to review scientific material relative to the medical effects of fluoride in drinking water supplies. The committee included recognized experts in bone metabolism, endocrinology, toxicology, and the metabolism of fluoride (TAB A). In addition a group of advisors unable to attend the two day meeting was asked to review documents and to provide counsel in regard to the committee's recommendations. Each participant received reference material in advance of the meeting. (The final report was circulated for comment and revision prior to development of the final draft.)

In its discussion the committee focused on recognized or potential adverse effects of fluoride on health, including the highest no observed effect exposure levels, or the lowest observed levels, the various persons and age groups considered to be at risk for potential effects, and the margin of safety required to assure that "the no adverse effect" level had been determined.

The committee recognized that inclusion of a substance in a primary regulation requires compliance, whereas secondary regulations are not federally enforceable.

The committee's discussion covered a wide range of topics including the metabolism of fluoride, the effects of pharmacological doses of fluoride on

skeletal tissue, fluoride effects on soft tissues, and the epidemiology of disease and mortality statistics as related to fluoride in drinking water.

Salient features to emerge from these discussions include the following:

1. There are approximately 3,437 communities in the U.S. whose water fluoride content is between 1-2 ppm, 944 between 2-3 ppm, and 710 with fluoride content 3-4 ppm. Only 250 communities have fluoride content in excess of 4 ppm. There are communities with higher than optimal fluoride content in Texas, and the south, but others are found in other locations as well.

2. The committee reviewed a series of studies collected by the International Agency for Research on Cancer and published in 1982 (Vol. 27). Also reviewed were reports dealing with mortality in cities prior to, and following fluoridation, the lack of mutagenic effects of fluoride in tissue culture systems, and a recent study demonstrating no adverse effect in chromosomes in testes and marrow cells from Swiss mice maintained at various fluoride intakes for several generations (G. R. Martin, et al, NIDR, NIH). This latter study found that fluoride does not alter chromosome aberration rates.

   The committee concluded that available data indicate no demonstrable effect of fluoride as a mutagen or carcinogen. Also, using standardized

mortality rates, there appears to be no relationship between carcinogenesis and the advent of fluoridation or overall disease related mortality and fluoride supplementation.

3. Ingested fluoride is assimilated into calcified tissues; 99% of fluoride is in the skeleton and teeth. The aorta is the only other tissue which exhibits high (25-90 ppm) fluoride mainly in calcified deposits. Soft tissues contain approximately 1 ppm or less, the kidney having relatively higher levels due to urine in tubules and collecting ducts.

Fluoride in bone increases with age and linearly in relation to fluoride intake. As renal function declines, with specific diseases or with normal aging, plasma and bone fluoride content both increase (Smith). However, individual variation in skeletal fluoride content may approximate 50% at all ages. Thus, any generalization on skeletal fluoride accumulation in large populations based on intake may be quite imprecise. Available data suggest that radiologically detectable osteosclerosis appears in bone fluoride content (dry, fat free) in excess of approximately 2500 ppm which corresponds to chronic ingestion of approximately 5 ppm in the water supply. Clearly this estimate is dependent on several variables including total dietary fluoride, age, renal function, and the influence of other substances on fluoride absorption and bone mineral turnover.

Studies of fluoride accumulation by the thyroid, based on studies with F^{18}, demonstrate no active accumulation: retained isotope was that in thyroid blood only.

4. The committee examined reports relating dietary fluoride to the cardiovascular system. No consistent effect of sodium fluoride administration (25 mg/d) on cardiovascular function, EKG, or cardiac rhythm has been observed at three major centers: Mayo Clinic, Henry Ford Hospital, and the Hines, VA Hospital. Reports of chronic industrial exposure do not indicate a toxic effect of fluoride on the cardiovascular system. Acute poisoning, however, can have such an effect. The committee reviewed reports of Okoshi et al, where children and adults drinking water containing 1.9-4.8 ppm had evidence of arrhythmias and myocardial disease. In the absence of more detailed study it was concluded that a variety of contributing factors would have to be examined before a direct relationship between fluoride intake and myocardial function could be established.

Finnish workers examined the incidence of heart disease in communities with water fluoride content varying from 0.05 to 2.57 ppm. Water magnesium varied directly with fluoride. The percentage of men with heart and other circulatory diseases was lowest in the districts with highest water fluoride and magnesium. While magnesium may play

an independent role, the higher fluoride intake did not appear injurious to the cardiovascular system in this study.

5. The effect of pharmacologic doses of NaF (30 mg/d, approximately 13 mg/F) ingested for over two years by osteoporotic patients, on the histology of bone was reviewed in depth. These studies, now in progress, indicate that:

   a. At a dose of 0.1-0.4 mg/kg F/day with 1.5 gm total calcium intake and 400 I.U. Vitamin D, iliac crest bone biopsies reveal focal increase in bone mass, loss of cortical-trabecular demarcation, osteoblastic stimulation, and an absence of changes in bone marrow. Studies at the Hospital for Special Surgery, NYC, do not show the induction of osteomalacia; however, the presence of focal unmineralized areas of osteoid "osteoid links" does suggest a mineralization defect. Periosteal new bone formation as seen in animal studies was not seen in the human biopsy material. Correlation of high dose fluoride intake in these investigations (as compared to lower levels in drinking water) with bone fluoride content is not yet available.

   b. More active osteoid formation has been observed in iliac crest bone biopsies obtained at Henry Ford Hospital.

c. Results communicated to the committee from the current Mayo Clinic osteoporosis study (Dr. Riggs) indicate that at therapeutic doses the incidence of postmenopausal fracture may be diminished. Other studies show no effect of fluoride at 1 ppm (drinking water) on incidence of fracture.

d. It is uncertain whether fluoride in therapeutic doses (approximately 0.2-0.4 mg/kg/day) increases porosity of cortical bone while increasing the mass of trabecular bone. No increase in cortical porosity was observed in iliac crest biopsies at the Hospital for Special Surgery. Dambacher et al, used X-ray techniques to demonstrate a significant decrease in metacarpal and femoral diaphyseal cortex, raising the possibility (Riggs, et al) that fluoride could protect against vertebral fracture but not protect, or even increase, the risk of femoral fracture. The status of parathyroid function in subjects chronically treated with high doses of fluoride is unclear.

Data are lacking on the long-term effects of therapeutic (pharmacologic) doses of sodium fluoride on skeletal tissue in osteopenic subjects. Side effects of therapy at the 0.2-0.4 mg/kg/day and above mainly include arthralgias and GI irritation. The mechanism causing

arthralgias is unknown. Epigastric pain, nausea, vomiting, and occasionally anemia due to blood loss are presumably the result of fluoride effects on the gastric tissue.

6. A review of the effects of fluoride supplements in animals (Dr. Shupe) disclosed:

   a. Marked increase in new bone formation at high dose levels, mainly periosteal growth.

   b. Increased fluoride deposition in young and growing animals as opposed to mature animals.

   c. Interspecies variation in response to fluoride supplements as well as variation ____(%) of uptake by different bones (pelvis, mandible, vertebrae, femur).

   d. The appearance of unequivocal changes in bone histology at a fluoride concentration of less than about 2500 ppm.

7. A review of studies correlating radiologic evidence of osteosclerosis with fluoride intake was presented to the committee:

a. Leone, et al, 1955: Excessive fluoride (8 mg/l) in drinking water may produce roentgenographic evidence of bone changes but:

(1) in 10-15% of all those exposed over a period of many years;

(2) changes which are slight or difficult to recognize;

(3) X-ray findings were unassociated with other physical findings, except for dental mottling;

(4) and may not occur even though the fluoride content of bone may be six times that of normal bone.

b. Stevenson and Watson (1957) evaluating X-rays at the Scott and White Clinic (Temple, Texas) 1943-1953, found osteosclerosis recorded on X-ray in 23 of approximately 170,000 X-ray examinations of the spine and pelvis. For those 23 patients, drinking water fluoride content varied from 4-8 ppm. Four ppm was described as the threshold following chronic exposure for the appearance of osteosclerosis.

c. A study of industrial fluorosis (Franke, et al) (1978) found vague symptoms of stiffness at a level of 3500-4500 ppm in bone, with stage 1 X-ray changes present at fluoride concentrations of 6000-7000 ppm in bone; stage 0-1 evidence of osteosclerosis at 5000-5500 ppm in bone.

8. Wenzel, et al (19__) have reported skeletal development in 12-14 year-old girls to be unrelated to dental fluorosis when studied in two Danish areas continuing 0.2 and 2.4 ppm fluoride in drinking water. An as yet unpublished study in a typical high fluoride area is quoted by these authors as showing a relationship between fluoride intake and skeletal maturity (Arch. Oral. Biol., in press) at a level of 3.6 ppm.

9. The definition of "adverse health effects" as related to fluoride was assumed by the group to include:

   a. death (acute poisoning)
   b. gastrointestinal hemorrhage
   c. gastrointestinal irritation
   d. arthralgias
   e. crippling fluorosis

With respect to fluoride in drinking water, GI effects were thought not to occur. Osteosclerosis was not considered an adverse health effect; osteomalacia was not considered an adverse effect based on the limited data available to the committee. A radio-dense skeleton without soft tissue changes (e.g., calcified ligaments) was not considered an adverse effect on health as opposed to crippling fluorosis which includes both hard and soft tissue lesions.

The committee emphasized the current lack of data relative to:

1. The effect of supraoptimal fluoride intake on bone turnover in children and the relationship of moderate to severe dental fluorosis on skeletal development.

2. The need to confirm or refute Japanese studies implicating chronic fluorosis and myocardial disease (Takamori, Tokushima, J. Experimental Med. 2:225, 1955).

In 1980, the National Academy of Sciences reported adequate and safe intake for fluoride as follows:

Infants less than 6 mo.----------0.1-0.5 mg/day

Infants, 6-12 mo.----------0.2-1.0 mg/day

Children, 1-3 yrs.----------0.5-1.0 mg/day

Children, 4-6 yrs.---------- 1.0-2.5 mg/day

Children greater than 7 yrs.------ 1.4 mg/day

Certainly, such recommendations are dependent upon total intake, both water and diet, and presume a normal nutritional status with regard to other minerals and bone seeking substances.

The Drinking Water Advisory Council (EPA) met on October 26, 1982, to provide recommendations for a response to the South Carolina petition seeking to remove fluoride from primary drinking water regulations. The committee voted to continue the primary MCL based on adverse health effects, and a secondary MCL based on cosmetic effects. The secondary MCL was recommended at 2 mg/L. The committee split 6-6 as to whether the fluoride primary regulation should be at 4 mg/L or at a value to be determined in the range of 4-8 mg/L.

This (PHS) committee, after reviewing nondental toxicity of fluoride, generally agrees with the recommendations of the Drinking Water Advisory Council that there be a primary regulation based on health effects.

In response to the EPA request concerning the "no known or anticipated adverse effect level with a margin of safety," the committee concluded that the fluoride content of drinking water should be no greater than:

1. Twice the current optimal level (1.4-2.4 mg/l) for children up to and including age 9, and, On Page 423 of the transcript, Cotruvo states this really means an MCL of 2.0 mg/l. Mary concurred
2. No greater than four times the optimal level for older persons (2.8-4.8 mg/l).

The committee favors continuation of fluoride in the primary regulations because of lack of information regarding fluoride effect on the skeleton in children (to age 9) over 3 ppm, and potential cardiotoxic effects at that level. While not specifically addressing dental effects, there was a consensus that mottling or pitting of teeth could represent as yet unknown skeletal effects in children and that severe dental fluorosis per se constitutes an adverse health effect that should be prevented. There was some sentiment (especially among the pediatricians) in the committee that the age limit for children in 1. should be as high as 18 years because of continued rapid bone development between ages 9 and 18; however, the lower value ultimately was agreed to.

In adults, fluoride intake in excess of 5 ppm is known to be associated with osteosclerosis. (see p. 12)

The committee strongly recommends that the PHS and the EPA join to enlarge the body of information relative to skeletal maturation and growth in children ingesting more than twice the recommended daily intake of fluoride.