REPORT TO THE SURGEON GENERAL:

By the Ad Hoc Committee on the

NON-DENTAL HEALTH EFFECTS OF FLUORIDE IN DRINKING WATER

Based upon discussion and recommendations made during a meeting held in Bethesda, Maryland on April 18-19, 1983.

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

An ad hoc PHS committee on dental fluorosis, reviewing the scientific aspects of epidemiologic studies related to fluoride in drinking water, subsequently reported (July 1982), in effect, that twice optimum (1.4-2.4 mg/l) is a conservative 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 (July 30, 1982) agreed 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." These statements were contained in the ad hoc PHS committee report.

In January 1983, EPA requested that the PHS conduct a review to determine the level at which adverse non-dental (medical) health effects may result as a consequence of fluoride in natural drinking water supplies and the margin of safety that 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, five issues identified by the EPA were:

1. Could fluoride have any adverse or potential adverse effect on health, specifically with reference to potential non-dental toxicity?

2. Do the levels of fluoride in drinking water meet the criteria of the Safe Drinking Water Act, e.g., "have any known or anticipated adverse effect on the health of persons"? What, if any, are those potential adverse health effects?

3. What would be the "highest no observed adverse effect exposure level" and/or the "lowest observed effect level?"

4. Which persons in the general population would be considered most sensitive and for what reason; age, severe disease, high water intake, etc?

5. What margin of safety would be appropriate to assure that the "no-known or anticipated adverse effect level" had been determined?

The current fluoride maximum contaminant level of 1.4-2.4 mg/l was established in 1975 as an interim primary regulation. The EPA at that time considered the potential effects of fluoride above two times the optimum to be adverse health effects. These included increased evidence of dental fluorosis (at 2 mg/l or above), osteosclerosis (at 8 mg/l or above), and crippling fluorosis (at 20 mg/l or above).

In March 1983, at the direction of the Surgeon General, an ad hoc committee was organized to review scientific material relative to the medical (e.g., excluding dental) effects of fluoride in drinking water supplies. The committee included experts in bone metabolism, endocrinology, toxicology, and the metabolism of fluoride. In addition, a group of advisors unable to attend the two day meeting (April 18-19, 1983) were 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 and the final draft was circulated for comment and revision prior to development of the final report.

In its discussion the committee focused on recognized or potential adverse effects of fluoride on health, including the highest "no observed adverse effect" exposure levels, and the lowest observed effect 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'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. The committee reviewed a series of studies collected by the International Agency for Research on Cancer and published in 1982.[1] 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 on chromosomes in testes and marrow cells from Swiss mice maintained at various fluoride intakes for several generations. This later study found that fluoride does not alter chromosome aberration rates.[2] Also, using standardized mortality rates, there appears to be no relationship between carcinogenesis or overall disease related mortality since fluoride supplementation was initiated.[3] The committee concluded that available data indicates no demonstrable effect of fluoride as a mutagen or carcinogen. This is consistent with the conclusion regarding fluoride and cancer reached by the Governor's Task Force on Fluorides, State of Michigan, 1979.[4]

2. Once ingested, fluoride is assimilated into calcified tissues; 99% of retained fluoride is in the skeleton and teeth. The aorta is the only other tissue which exhibits high (25-90 ug/g) fluoride mainly in calcified deposits. Soft tissues contain approximately 0.1 ug/g or less, the kidney having relatively higher levels due to urine in tubules and collecting ducts.

3. Fluoride in bone increases with age and linearly in relation to fluoride intake. As renal function declines, due either to diseases or with aging, plasma and bone fluoride content both increase. However, within a specified range of intake, skeletal fluoride accumulation may vary as much as + or -50% at all ages.[5] Thus, any extrapolation about skeletal fluoride accumulation in large populations based on intake may be quite imprecise. Available data suggests that radiologically detectable osteosclerosis sometimes appears in bone with fluoride content (dry, fat free) in excess of approximately 2,500 ppm, which corresponds to chronic ingestion of approximately 5 ppm in the water supply.[6] Clearly, this estimate is dependent on several variables including total dietary fluoride, rate of intake, age, renal function, and the influence of other substances on fluoride absorption and bone remodeling.

4. Studies of fluoride accumulation by the thyroid, based on studies with F-18, demonstrate no active accumulation: retained isotope could be accounted for by thyroid blood flow.[7] There is no evidence of an adverse effect of fluoride in drinking water on thyroid function.

5. The committee examined reports relating dietary fluoride to effects on the cardiovascular system.[8] No consistent effect of sodium fluoride administration (25 mg/day) on cardiovascular function, EKG, or cardiac rhythm have 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, may have such an effect.

   The committee reviewed reports of Okushi et al, where children and adults drinking water containing 1.9-4.8 ppm had evidence of arrhythmias and myocardial disease.[9] In the absence of more detailed and corroborating studies, it was concluded that a variety of contributing factors would have to be controlled before a relationship between fluoride intake and myocardial function could be validly proposed. Finnish workers examined the incidence of heart disease in communities with water fluoride content varying from 0.05 to 2.57 ppm.[10] Water magnesium varied directly with fluoride content. 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 detrimental to the cardiovascular system in this study.

6. The effect of pharmalologic doses of NaF (60 mg/day, approximately 27 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 1 mg/kg F/day (0.45 mg F/kg/d) with 1.5 gm total calcium intake and 400 I.U. Vitamin D, iliac crest bone biopsies reveal a focal increase in bone mass. Other microscopic findings include loss of cortical-trabecular demarcation and osteoblastic stimulation of bone formation. There are no recognizable changes in the hemopoetic tissues. 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 lakes", does suggest a mineralization defect. Periosteal new bone formation as seen in animal studies was not seen in the human biopsy material. Correlation of pharmacologic high dose fluoride intake in these investigations (as compared to much lower levels in drinking water) with bone fluoride content is not yet available.

   b. The formation of poorly mineralized matrix has been observed in iliac crest bone biopsies obtained at Henry Ford Hospital. This is not considered an osteomalacic effect.

   c. Preliminary results communicated to the committee from the current Mayo Clinic osteoporosis study (Dr. Lawrence Riggs) indicate that at therapeutic doses the incidence of postmenopausal fracture may be diminished. Other studies demonstrate no effect of fluoride at 1 ppm on the 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 at the same time 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, thus raising the possibility (Riggs, et al) that fluoride could protect against vertebral fracture, but might not protect, or perhaps, even increase, the risk of femoral fracture.[11] The status of parathyroid function in subjects chronically treated with high doses of fluoride is uncertain.

Since the current controlled studies are still in progress, data are lacking on the long-term effects of therapeutic (pharmacologic) doses of sodium fluoride in skeletal tissue in the osteopenic subject. Side effects of therapy at 0.2-0.4 mg/kg/day and above include arthralgias, epigastric pain, nausea and vomiting, and occasionally anemia due to blood loss as an effect of fluoride on the gastric tissue. However, gastic irritation has been lessened by administration with food and in gelatin capsules.

7. A review of the effects of fluoride supplements in animals disclosed:

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

   b. Increased fluoride deposition in the skeleton of young and growing animals as compared to mature animals.

   c. Interspecies variation in response to fluoride supplements as well as variation (25-35%) in fluoride uptake by diaphyseal and metaphyseal regions of different bones.

   d. The appearance in animals of unequivocal changes in bone histology at a fluoride concentration of less than about 2,500 ppm (fat free bone).[12]

8. 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, (10 times optimum for the region studied), may produce roentgenographic evidence of bone changes, but:

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

      (2) radiologic changes which were 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.[13]

   b. Stevenson and Watson (1957) evaluated x-rays at the Scott and White Clinic (Temple, Texas) 1943-1953, and found osteosclerosis recorded on x-ray in 23 of approximately 170,000 x-ray examinations of the spine and pelvis).[14] These 23 patients, aged 44-85, lived their entire lives in areas where the fluoride content of drinking water water was 4-8 ppm, (5-10 times the optimum of 0.8 ppm for the region). Four ppm was considered the threshold following chronic exposure for the appearance of osteosclerosis.

      The incidence of this condition in persons drinking 4 ppm, and how it compares to that in the general population drinking lower levels of fluoride, cannot be determined from this report. However, with the exception of one case, (an individual drinking 4 ppm for 79 years), no cases were detected in any individuals drinking water with six times optimal or less fluoride.

   c. A study of industrial fluorosis found vague symptoms of stiffness at fluoride levels of 35,000-45,000 ppm in bone, with stage 1 x-ray changes present at fluoride concentrations of 6,000-7,000 ppm in bone; stage 0-1 radiologic evidence of osteosclerosis at 5,000-5,500 ppm in bone.[15]

9. Wenzel, et al, have reported that skeletal development in 12-14 year old girls was unrelated to dental fluorosis when studied in two Danish areas continuing 0.2 and 2.4 ppm fluoride in drinking water.[16] A recently published study comparing skeletal maturity in high and low fluoride areas of Tanzania is reported showing an inverse relationship between fluoride water content and skeletal maturity at a level of 3.6 ppm.[17] Again, the influence of other environmental factors was not clear in this study.

10. 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

GI effects were thought not to occur at fluoride levels found in drinking water. Mild osteosclerosis was not considered an adverse health effect in adults: increased tissue osteoid 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 information relative to:

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

2. frequently cited but circumstantial and isolated Japanese studies suggesting a relationship between fluoride intake and myocardial function.

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.	0.5-1.5 mg/day
Children, 4-6 yrs.	1.0-2.5 mg/day
Children greater than 6 yrs.	1.5-2.5 mg/day

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

In consideration of the foregoing and in response to the EPA request, the committee concluded that:

1. It is inadvisable for the fluoride content of drinking water to be greater than twice the current optimal level (1.4 - 2.4 mg/l) for children up to age 9 in order to avoid the uncosmetic effects of dental fluorosis. This conclusion coincides with the recommendations of the Surgeon General relative to the dental effects of naturally occurring fluorides.

2. The fluoride content of drinking water should not be greater than four times the optimal level for any community water supply. This conclusion recognizes that, fluoride intake from water between 5.0 and 8.0 mg/l (4 times - 10 times optimum) has been associated, in a very small number of subjects, with the radiologic appearance of early osteosclerosis, which while not an adverse health effect, is however, an indicator of demonstrable osseous changes not to be anticipated at lower levels (less than 4 times optimum) of fluoride.

3. The difference between 4 times and 10 times optimum represents an adequate margin of safety unless further research warrants reconsideration of these levels. There exists no directly applicable scientific documentation of adverse medical effects at levels of fluoride below 8 mg/l (ppm). Therefore, it can be concluded that 4 times optimum in U.S. drinking water supplies is a level that would provide "no known or anticipated adverse effect with a margin of safety."

4. The effects of various levels of fluoride intake on rapidly developing bone in young children are not well understood. Also, the modifying effects of total intake, length of exposure, other nutritional factors and debilitating illness are not well understood. Therefore, 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 the recommended daily intake of fluoride.

(Purported "optimum" is 0.7 - 1.2 ppm)

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