



COMMONWEALTH of VIRGINIA

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FLUORIDE IN DRINKING WATER

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Introduction

This report was developed in response to requests from within the Health Department for a review of the available literature relating to the health effects of fluoride. It is not the purpose here to review extensively information related to the question of the efficacy of fluoride in preventing dental caries, though the subject will be touched upon. Particular emphasis has been placed upon those studies which relate to health effects reported to be associated with the 1-10 ppm fluoride level in drinking water. Such information should be helpful to those who must decide whether fluoride levels in excess of 1.8 ppm in drinking water pose adverse health effects of a magnitude sufficient to warrant fluoride reduction.

Fluoridation of public water supplies at the 0.8-1.2 ppm level is widespread in the United States, a practice which has increased continually since 1945 when it was first introduced in Grand Rapids, Michigan. According to Sanders (1980), approximately 110 million Americans drink water that is naturally or artificially fluoridated. The other half of our population does not consume fluoridated water. Approximately 73 million of the latter live in communities which have chosen not to fluoridate and 37 million lack centralized water supplies for fluoridation. A large body of information has developed on the subject during the years as fluoridation has become more widespread. There are several scientific studies and many government reports on the subject. The same body of scientific information finds its

expression repeatedly in many settings. Unfortunately, while there is a substantial body of scientific information not all parties agree as to its interpretation and much additional basic research is sorely needed to pin down the biological effects of fluoride and the levels at which adverse health effects would be expected. Every effort has been made in this report to adhere to the ideal of presenting only scientific information and discussion pertaining to it. The report necessarily strives within the constraints of time to condense information and to identify and critically evaluate several of the studies which show or carry the implications of health effects in man. This report is not complete. The evaluation of the health effects of fluoride must continue as long as the substance is found in drinking water, tooth paste, mouth rinses, etc., and concern exists as to its safety.

This review is divided into sections covering not only dental effects but skeletal system effects, kidney effects, Down's syndrome, mutagenesis, DNA studies and cancer. There are important studies in all these areas and it is important to consider all the information in reaching a general understanding of the health effects of fluoride.

Health Effects

The World Health Organization (1970) has discussed at length certain aspects of the health effects of fluoride. This volume has been reviewed and an attempt made to identify, by subject author(s) and page number, key statements which address the question of health effects observed at various fluoride concentrations. Many of these

key statements are quoted in order to minimize ambiguity that might be introduced by paraphrasing. While statements by the various authors are not always consistent, one can gain from these statements an understanding of the effects on bone and teeth of fluoride at various levels.

A summary relationship of concentrations or doses of fluoride (F) to biological effects as given in this volume is tabulated as follows:

A. Singh and S. S. Jolly, p. 225.

<u>Concentration or Dose of Fluoride</u>	<u>Medium</u>	<u>Effect</u>
2 parts per 1,000 million	Air	Injury to vegetation
1 ppm	Water	Dental caries reduction
2 ppm or more	Water	Mottled enamel
5 ppm	Urine	No osteosclerosis
8 ppm	Water	10% osteosclerosis
20-80 mg/day or more	Water or air	Crippling fluorosis
50 ppm	Food or water	Thyroid changes
100 ppm	Food or water	Growth retardation
More than 125 ppm	Food or water	Kidney changes
2.5-5.0 g	Acute dose	Death

Dental Effects

Additional information relating to dental effects follows:

"During the period of tooth formation, the ingestion of amounts of waterborne fluoride as low as 1 ppm may produce slight white spots in the enamel surfaces in a few cases." S. M. Weidmann and J. A. Weatherell, p. 116.

"Moreover, an objectionable degree of mottling is observed only when fluorides are consumed during the ages of about 0-12 years and at levels in excess of 2.0 ppm." N. C. Leone, p. 274.

"These early (1916) American investigators found that when water contained concentrations substantially greater than 2 ppm F, there often developed dental defects, ranging from barely detectable white spots called dental mottling at the lower levels to unsightly brown, stained, hypocal-

cified or hypoplastic teeth at higher levels, i.e., 4-8 ppm F." N. C. Leone, p. 277.

"Dean and his colleagues (Dean, 1946) investigated the threshold of dental fluorosis in the mid-western region of the USA, and set the borderline limit for the appearance of dental fluorosis in the vicinity of Chicago at 1.0-1.5 ppm fluoride. But in Japan, in an investigation around the Kyoto District, it seems that the corresponding borderline limit is 0.8-1.1 ppm." G. Minoguchi, p. 294.

"The minimal threshold value at which a just perceptible change appears in the developing enamel of the permanent teeth was found to be 1.0-1.1 ppm for the people in the USA living in the temperate zone. It is only after the fluoride concentration in drinking water exceeds 1.4-1.6 ppm that the first signs of more serious dental fluorosis appear: some of the teeth of a few members of the population then show circumscribed spots, colored light-yellow to brownish. When the fluoride content exceeds 2.0 ppm, then brownish spots, varying from small to large in size, can be seen on numerous teeth in the great majority of the members of the exposed community. When the fluoride content is more than 2.5 ppm, the enamel loses its smoothness: signs of serious dental hyperfluorosis appear, with hypoplastic zones and an often quite dark discoloration affecting extensive areas of the enamel of several teeth in the persons affected." P. Adler, p. 323.

Dean (1936) provides an excellent chart and comment on extent of mottling in relation to water fluoride level:

"From the continuous use of water containing about 1 ppm, it is probable that the very mildest forms of mottled enamel may develop in about 10% of the group. In waters containing 1.7 or 1.8 ppm, the incidence may be expected, to rise to 40 or 50%, although the percentage distribution of severity would be largely of the 'very mild' and 'mild' types. At 2.5 ppm an incidence of about 75 to 80% might be expected, with possibly 20 to 25% of all cases falling into the 'moderate' or a severer type. At 4 ppm the incidence is, in general, in the neighborhood of 90% and as a rule 35% or more of the children are generally classified as 'moderate' or worse. In concentrations of 6 ppm or higher an incidence of 100% is not unusual." p. 1272.

"From observations that I made in areas of relatively high fluoride concentration (more than 4 ppm fluorine) there is sufficient evidence to suggest that there is an apparent tendency toward a higher incidence of gingivitis." p. 1271.

According to Schlatter (1977):

"The tissues which are most susceptible to the effects of fluorides are the growing teeth. This takes place in man during the first eight to ten years of life. Once the ameloblasts have ceased to function, the teeth can no more be affected by fluorides." p. 7.

Sanders (1980), however, indicates that fluoridated water is beneficial to some extent in reducing tooth decay in older people.

One perceives therefore from a variety of sources that the incidence and degree of dental fluorosis or mottling observed in populations is related to the concentration of fluoride in drinking water, and that significant mottling would be expected to develop in youths after several years of exposure to water containing more than 2 ppm fluoride. More substantial mottling would be expected consequent to exposure at 4 ppm and up.

There are those who might debate whether mottling of teeth constitutes an adverse health effect. The conclusion reached likely would be dependent upon the extent of mottling. Mottling certainly can be adverse to one's appearance and hence to one's psychological health and happiness. Dental surveys should be taken in those Virginia communities where drinking water contains high natural fluoride levels to determine if mottling is more widespread than normal. Such information could be helpful in determining whether to defluoridate the drinking water.

Skeletal Effects

Statements on this subject from the World Health Organization (1970) are provided as follows with chapter author(s) and page numbers:

"The precise dose of ingested fluoride or inhaled fluoride which results in well recognized skeletal changes has not been fully evaluated. However, certain broad conclusions are possible at this stage. In fluoridation studies in adults which envisage a daily intake of 0.5-2 mg of fluoride, no evidence of storage, as defined in terms of abnormal density of bone, has ever been demonstrated. At higher levels of ingestion--from 2 to 8 mg daily--when signs of fluorosis appear in teeth mineralized during the ingestion period, certain other factors (climatic conditions, malnutrition, age, storage, other constituents of water and, possibly, individual variations in absorption) may be involved. Under such conditions and over a number of years, skeletal fluorosis may arise, characterized by an increased density of bone and demonstrated in adults radiographically. The data put forward by McClure et al. (1945), although no longer regarded as accurate, indicate that the limit of total fluoride which may be ingested daily without hazardous body storage is of the order of 4-5 mg daily. In areas of endemic fluorosis, levels of ingestion of fluoride from diet and water over 8 mg daily are common, although in certain regions of India, changes typical of skeletal fluorosis have been stated to occur at estimated lower dosages. (Singh et al., 1962b)." A. Singh and S. S. Jolly, p. 239.

For the benefit of the reader the standard 70 kg man drinks approximately 1.5 liters of water daily and consumes 0.7 liters via food ingested (Kinsman, (1957)); 1 ppm fluoride water contains 1 mg fluoride per liter.

"The physiological effects of water-borne fluoride on the skeleton are a resultant of the effects on the chemistry, morphology, histopathology and x-ray density, and integrity or structure of both the inorganic and the organic phase of bone. In addition, the interplay of bone remodelling, fluoride deposition and mobilization may also influence skeletal physiology or function following fluoride exposure. It will be indicated that the various parameters mentioned do not interfere with the normal physiology of the skeleton in man ingesting water containing up to 4 ppm F and indeed up to 8 ppm F." I. Zipkin, p. 185.

On the subject of skeletal fluorosis:

"The most obvious symptom of this condition is the pathological growth of exostoses, the sites and forms of which

are many and various. In man, these may occur after long periods of fluoride ingestion at levels of 4-8 ppm or above in water." S. M. Weidmann and J. A. Weatherell, p. 116.

"Geever et al (1958b) made autopsy studies of 99 bones from 37 persons who had resided 10 years or more in communities where the drinking water contained 1-4 ppm of naturally occurring or artificially added fluoride and 33 controls from areas where the drinking water contained less than 0.5 ppm fluoride. The microscopic examination showed no significant difference between the fluoride-exposed group and the control group. It is, therefore, possible to conclude that the histopathological changes in endemic fluorosis occur only at higher levels of intake than 1-4 ppm." A. Singh and S. S. Jolly, p. 244.

Concerning crippling fluorosis:

"This advanced stage of fluoride intoxication results from the continuous exposure of an individual to 20-80 mg of fluoride ion daily over a period of 10-20 years. Such heavy exposure is associated with a level of at least 10 ppm in the drinking water supply." A. Singh and S. S. Jolly, p. 246..

Crippling fluorosis is a serious illness often presenting the grim picture of a bent posture accompanied by severely restricted bodily movements.

There is evidence that fluoride may be beneficial in preventing osteoporosis. Osteoporosis is defined by Dorland's Illustrated Medical Dictionary, 25th ed., as "abnormal rarefaction of bone, seen most commonly in the elderly. Depending upon the extent of demineralization of bone, it may be accompanied by pain, particularly of the lower back, deformities, such as loss of stature and pathological fractures."

Referring again to information in the World Health Organization (1970):

"During the work on this monograph, new, well documented reports have appeared, giving further support to the theory

that a certain degree of fluoride saturation, or possibly other fluoride influence on the skeleton, may provide a partial protection against senile osteoporosis. Since this condition is very widespread, particularly in aging women, and often leads to serious fractures and to invalidism, further knowledge of the role of fluorides in skeletal biology is urgently needed." Y. Ericsson, p. 14.

It is important to note that the level of fluoride in drinking water that would be expected to have a beneficial effect where this condition is concerned would be higher than that which is considered optimal dentally. This is supported by the following statement:

"Actually, the accrued evidence points to a beneficial effect of fluorides on adult bone (Leone et al., 1955) and several clinical studies in which 20-60 mg of fluoride has been administered daily in the control of various bone and calcium-loss conditions bear out this concept (Leone, unpublished data; Purves, 1962; Rich, 1961; Rich & Ensink, 1961)." N. C. Leone, p. 275.

"Recognizable roentgenographic bone changes, attributed to high fluoride intake, have been identified and described by a number of authors, but such changes have never been observed in otherwise healthy subjects consuming a natural water supply containing less than 4 ppm fluoride (Azar et al., 1961; Roholm, 1937). The bone findings described in association with an elevated fluoride intake are increased bone density and coarsened trabeculation of a degree that may be desirable in our aging population." N. C. Leone, p. 275.

"Actually, this x-ray study (Leone et al., 1955) provided evidence, later supported by other studies (Leone et al., 1960; Stevenson and Watson, 1960) that the described 'fluoride bone effect' is in fact both beneficial and desirable in adult bone since it counteracts the osteoporotic changes of the aged and the effects of calcium loss disease (Leone et al., 1955; Rich, 1961; Rich and Ensink, 1961; McClure, McCann and Leone, 1958)." N. C. Leone, p. 280.

"A radiographic study of the hands and wrists of 2005 children, 7-14 years of age, residing in 3.5-5.5 ppm fluoride areas failed to demonstrate abnormal bone growth or developmental effects (McCauley and McClure, 1954)." N. C. Leone, p. 283.

"According to epidemiological population studies, no impairment of or effect on the general health status could

be detected among persons residing for an average of 37 years in areas where the water supply contains fluoride at the level of 8 ppm, and no systemic abnormalities or abnormal laboratory findings were observed that might be associated with ingestion of fluorides (Leone et al. 1954, 1955)." N. C. Leone, p. 280.

"Prolonged high fluoride uptakes up to 8 ppm do not affect morbidity or mortality (Leone et al., 1954; Geever et al., 1958a, Hagan, 1957; Knizhnikov, 1958)." N. C. Leone, p. 280.

"In summary, it is evident that except for dental changes, long exposure to fluorides at what might be regarded as 'high levels', i.e., 2-8 ppm F, does not produce harmful or otherwise abnormal effects in man but does in fact have an effect on adult bone that is beneficial and most significant to those persons in the postmenopausal or older age groups." N. C. Leone, p. 284.

Although the investigations cited thus far from the World Health Organization (1970) appear to give fluoride at levels commonly ingested a good rating except in relation to the question of dental mottling, this same document discusses the work of Hirata in the Kyoto District of Japan and reported that:

"He examined 270 schoolchildren afflicted with dental fluorosis in areas where the drinking water contained 1.0-5.0 ppm fluorine*, and then divided them into three groups, mild, moderate and severe, according to the degree of dental fluorosis, without reference to the concentration of fluorine in the drinking water. Blood analyses were made in these patients. No changes were determined in the mild group, but in the moderate group a decrease (less than 6000/mm³) in white blood corpuscles was seen in 21.8% and a decrease (less than 3000/mm³) in the neutrophil number was seen in 32.7%. In the severe group, 47.2% showed a decrease in white blood corpuscles and 41.2% a decrease in neutrophil number. However, such abnormalities were not found in pupils beyond the age of puberty. X-ray examinations were made of the bones of the arms and hands of 29 children who showed moderate or severe dental fluorosis and accompanying neutrocytopenia. Abnormal signs, such as hypertrophy of the cortex of bones, shadow increase in the

*This author uses the term fluorine, but from reading elsewhere in this text it appears he is referring to fluoride ion.

ossification centre of carpal bones, and serrating changes in the metaphyseal cartilage of the radius and ulna, were demonstrated. Thus, abnormal blood and x-ray findings were not observed in persons with mild dental fluorosis. However, the investigation was mainly conducted during 1947-49, when nourishment and other factors were less satisfactory in Japan. The results of Hirata's investigation emphasize that effects on the whole body should be considered, and the addition of fluoride to water to prevent tooth decay carried out with great care.

"A few years later, Hamamoto (1957) discovered that 58 persons out of the 517 residents in one district in Okayama Prefecture, where 0.1-13.0 ppm fluorine was found in the wells, had reduced mobility in several joints. He estimated the content of fluorine in the drinking water and examined roentgenograms of the bones, and reported that 21 out of 33 persons who had drunk water containing over 5.0 ppm fluorine for over 10 years showed osteosclerosis-like symptoms, as did 2 of 97 children under 10 years of age.

"From the above observations, it appears that in the Central District of Japan, in communities where water with a fluorine concentration of over 5.0 ppm was continuously used as drinking water for over 10 years, there was a risk of contracting osteosclerosis." G. Minoguchi, p. 295.

The weight of evidence as presented by the above investigators indicates that fluoride in drinking water at concentrations of up to 4 ppm would not be expected to have harmful or beneficial effects on the skeleton, although Singh and Jolly, p. 239, do indicate that ingestion of 2 to 8 mg a day over a number of years may lead to skeletal fluorosis.

In the range 4-8 ppm it appears that a certain fraction of the exposed population would be affected by skeletal fluorosis. Based upon the concepts conveyed regarding fluoride and osteoporosis, some people possibly would be benefited by the increased bone density resulting from fluoride exposure. According to Jowsey et al (1979), in a concluding statement from a review article on fluoride and osteoporosis:

"The preponderance of evidence suggests that administration of fluoride and calcium is an effective and relatively safe form of treatment for osteoporosis and would result in addition to the skeleton of a measurable amount of mechanically sound mineralized bone, thus reversing the osteoporotic process and preventing further fractures." p. 121.

The claim that fluoride is beneficial in osteoporosis is dubious, however. Marx (1978) in writing on behalf of the Ad Hoc Committee, Strategy Workshop for Osteoporosis, National Institutes of Health advises that fluoride may not be beneficial in this condition and that its use outside the investigational setting is not recommended. Currently, dental prophylaxis is the only use of fluoride approved by the Food and Drug Administration. Marx indicates that it is unknown whether fluoride increases bone strength and cites evidence indicating that high fluoride administration may actually decrease bone strength and may lead to an increased incidence of bone microfractures and macrofractures.

It is important to keep in mind the work of Hirata in Japan who reportedly observed in children decreased levels of white blood corpuscles and neutrophils and abnormal skeletal x-rays which correlated with the extent of dental fluorosis where fluoride was present in the drinking water at 1-5 ppm. While adverse nutritional or other factors may have played a contributing role, it is quite possible that similar poor nutritional conditions may exist in areas of Virginia where fluoride is present in the drinking water at 1-5 ppm. Inadequate nutrition is known to be a problem in certain areas of the state. Furthermore, within almost every area, for various reasons, there

are those individuals who are poor and undernourished. One might add, also, that inadequate nutrition is not limited to the poor.

Kidney

Schlatter (1977) reviewed several studies on the effect of fluoride upon the kidney. According to this review, acute fluoride exposure is nephrotoxic in humans and in animals. In rats 100 ppm fluoride in drinking water is nephrotoxic to a certain fraction of those exposed. Levels below 50 ppm gave no evidence of kidney damage in the reported study. Rats exposed to 20 ppm (equivalent to about 2 mg/kg body weight daily) for 6 months displayed no adverse macroscopic or histological effect of the kidney. In yet another study no effect on kidney, liver or adrenal gland was observed in rats administered 0.02, 0.2 and 2 mg/kg body weight daily for 210 days. However, in one study, an oral dose of 3.5 mg/kg body weight administered daily for 6 weeks resulted in some necrosis of the tubuli and liver cell degeneration. The reviewer indicates that epidemiological studies showed no prevalence of kidney disease among individuals living in areas where the water supply contained high levels of fluoride.

The World Health Organization (1970) indicates that:

"No renal pathology ascribed to fluoride has been found in experimental animals maintained for protracted periods on diets or drinking water containing 50 ppm fluoride or less. The borderline water concentration at which some individuals of certain species (but not all) exhibit changes is about 100 ppm..." Hodge and Taves, p. 251.

The view that low level exposure to fluoride exerts no adverse effects

upon the kidney has been challenged in the literature, however. Burgstahler (1977) described the results of two animal studies which indicated an adverse effect of low level fluoride upon the kidney. One of these, a study by Sullivan (1969), as discussed by Burgstahler, showed an average 48% reduction in the activity of the enzyme succinic dehydrogenase of the kidney of golden hamsters when these animals consumed drinking water containing 1 ppm sodium fluoride as compared to animals drinking fluoride free water. The second study, Manocha et al (1975), conducted on squirrel monkeys, revealed that such animals exposed to fluoride at the 1 ppm and particularly at the 5 ppm level in the drinking water over a period of 18 months exhibited cytochemical changes in the kidney. According to Manocha et al:

"In these animals, the glomeruli showed an increase in the activity of acid phosphatase and the enzymes belonging to the citric acid cycle and the pentose shunt, whereas lactate dehydrogenase, a representative of the anaerobic glycolytic pathway, remained unchanged or only slightly changed. These observations suggest that fluoride in concentrations as low as 5 ppm interferes to some extent with the intracellular metabolism of the excretory system." p. 343.

"Our cytochemical investigations on the nervous system, liver and kidney after prolonged periods (up to 14 months) of fluoride intake via the animals' drinking water, revealed that the nervous system was not affected at all by the intake of fluoride in concentrations as high as 5 ppm. The liver showed no significant changes, but the kidneys of the animals drinking water containing 5 ppm fluoride showed certain cytochemical characteristics which may be interpreted in terms of deleterious metabolic effects in the kidneys, which excrete most of the fluorides from the organism." p. 347.

In reference to the above two studies Burgstahler says:

"Thus, it is no longer possible to claim that 'it has never been demonstrated that pathological changes in the kidney can be produced by fluoride levels of less than 100 parts per million' in the drinking water or diet." p. 306.

In discussing the effects of fluoride upon the kidney, it seems appropriate at this point to indicate that whereas the kidney fulfills the important task of removing toxic substances, such as fluoride, from the system, there is the consequent danger of fluoride intoxication in those individuals with impaired renal function who ingest fluoride. Johnson et al (1979) advises:

"The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride." p. 290.

It is evident from this statement and from information which lead to it that fluoridated water poses an enhanced threat to those among the populace who have impaired kidney function.

Down's Syndrome (Mongolism)

Studies have been reported which indicate the possibility that Down's syndrome is related to fluoride in the drinking water. The entire question of Down's syndrome and fluoride exposure has been reviewed by Taves (1979). A summary of information presented by Taves is given as follows: Taves cites three studies of Rapaport covering the period 1956-1963 in which this investigator reported a dose-related association between fluoride and the incidence of Down's syndrome where fluoride levels in the drinking water ranged 0.1 to 2.6 ppm. The reported increase in Down's syndrome at the higher concentration level was nearly three-fold. These studies have been criticized on the basis of somewhat low percentage ascertainment of birth data and on the basis of whether the preferred methods of treating data and expressing results were used.

Taves cites a short-term epidemiological study by Needleman et al

in 1974 which concluded that an increase in Down's syndrome in excess of 20% could be ruled out.

Three case finding studies in Britain covering different fluoride concentrations in the water did not show an association with the incidence of Down's syndrome. Taves indicates that heavy drinking of tea (contains fluoride) in England may have obscured the results. He notes, though, that the absolute rates of Down's syndrome were the same as in a Massachusetts study.

Taves also cites two studies by Erickson in 1976 which reported no association between fluoride and Down's Syndrome. There are separate criticisms of these two studies. The first study is criticized for having low ascertainment of birth data. The second study had good ascertainment but revealed an 18% higher crude rate for Down's syndrome. Though this 18% was not statistically significant by itself, Taves indicates that such findings cannot be used to rule out a potential effect. Taves included comment on a study by Burgstahler in 1977 which claimed that the Erickson study confirms the work of Rapaport to the extent that younger mothers were found to be most affected in giving birth to individuals with Down's syndrome from fluoride exposure. However, Taves indicates this argument is based upon selective use of the data.

Taves' concluding statement on the question of fluoride and Down's syndrome is given as follows:

"In conclusion, the case for the claim that fluoridation leads to increased Mongolism is based on questionable and

selected data and the case against the claim is based on studies with short-term exposure, and on data which cannot rule out an increase for long-term exposure, particularly in young mothers. Further study would, therefore, seem to be in order on large populations with life-time exposure." p. 302.

Since it appears that a serious question remains concerning a possible causative relationship between fluoride ingestion and Down's syndrome, one would think that, in view of the widespread human exposure, efforts directed toward obtaining definitive results should have been undertaken or certainly should be in progress.

Mutagenesis

In reviewing the toxic effects of chemical substances, studies covering the potential mutagenic effects are certainly of great importance in the overall consideration. The implications of mutagenic effects particularly in relation to cancer and other pronounced or subtle health effects are generally recognized.

Information on mutagenesis has been reviewed by Waldbott et al (1978) and by Taves (1979). It is from these two sources that the other studies discussed below were identified and are commented upon.

Waldbott et al (1978) cite published work by Mohamed and associates showing that concentrations of hydrogen fluoride too low to cause visible tissue injury cause chromosomal alterations (this term being used loosely to cover all sorts of observable chromosomal changes, though there are specific terms for the different types of changes) in certain plants. This reference also cites publications showing that hydrogen fluoride increases genetic damage in Drosophila melano-

gaster (fruit fly).

Jagiello and Lin (1974) investigated the mutagenic potential of sodium fluoride on the female mammalian germ cell (oocyte) of the cow, ewe and mouse. In these studies a number of mutagenic type observations were made upon exposure of the isolated oocyte (in vitro study) in sodium fluoride containing medium. Also effects on mouse oocytes were assessed when the mice were administered sodium fluoride via subcutaneous injection of the maximally tolerable dose, 5 μ g/gm body weight (in vivo study). In the in vitro study mutagenic effects were observed in all three species of animal. In the cow oocyte, for example, clumping of chromosomes at meiosis was observed at the lowest sodium fluoride concentration employed, 0.01 mg/ml, equivalent to 4.5 ppm fluoride.

As stated in this paper:

"As a screening tool for inducing and detecting assessable in vitro meiotic abnormalities in oocytes, it would appear from these data that those of the ewe and cow are more sensitive than those of the mouse. Some of the types of abnormalities seen in all three species have been considered significant to the development of abnormal progeny, seen as abortuses and viable offspring in human populations."
p. 234.

Jagiello and Lin stated furthermore that sodium fluoride can be a potent meiotic mutagen in the particular in vitro studies reported in this paper. With regard to the in vivo mouse study, they indicate that the data suggest only a minor adverse effect on oocyte meiotic maturation. The authors endeavor to suggest reasons why fluoride did not have a pronounced effect in vivo, but the actual reason is unknown.

The metabolic fate of fluoride in the whole animal may have prevented

its reaching the oocyte in sufficient concentration to mimic the in vitro effect. If fluoride causes mutagenic effects in vitro, then relatively minor findings in vivo in the mouse would not preclude damage to other types of cells, or damage to oocytes at higher fluoride concentrations or prolonged exposure to lower levels. It should be noted that the cow and ewe were not studied in vivo and oocytes from these species as indicated above were found to be more susceptible to the adverse in vitro effects of fluoride.

Leonard et al (1977) observed leucocytes in cows suffering from fluorosis. These studies did not reveal a statistically significant difference in total chromosomal and chromatid aberrations; however, although the chromatid aberration rate was the same as in the control animals the chromosomal aberration rate was over twice that of the control. The authors, however, did not consider the observed overall aberration rate increase to be significant. The authors did qualify the conclusions somewhat by saying that lymphocytes bearing chromosomal aberrations may have been eliminated from the host system. In addition to their own studies, these investigators briefly reviewed other literature on fluoride mutagenesis covering both positive and negative studies. With reference to the cited studies, these authors wrote:

"These data suggest that inorganic fluor compounds represent a potential genetic hazard to mammals." p. 240.

Waldbott et al (1978) also reviewed the work of Mohamed and Chandler (1977) on mutagenic studies in mouse bone marrow cells and spermatocytes when sodium fluoride was administered in the drinking water

at varying concentration. This study showed statistically significant increases in chromosomal aberrations in both types of cells even at drinking water levels as low as 1 ppm sodium fluoride.

It must be noted that this latter study was published in the proceedings of a subcommittee of the U. S. House of Representatives and has not been published in the scientific literature. Hence, it has not successfully met peer review. The National Dental Institute, Martin et al (1979), conducted a study very similar to that of Mohamed and Chandler with apparent effort to establish the validity of the findings of these investigators and reported no statistically significant effect of fluoride in causing chromosomal aberrations in mouse bone marrow cells or spermatocytes.

Taves (1979) has reviewed the findings of a number of fluoride mutagenic studies. Taves cites the Mohamed and Chandler study referenced above as indicating a mutagenic effect of fluoride. However, he does present criticisms of this work. With regard to the plant mutagenic work of Mohamed and associates, Taves cites an unpublished study by Temple and Weinstein which:

"...confirmed the increased frequency of bridge and fragmentations of chromosomes in onion root tips when grown in 10^{-2} M fluoride, but did not confirm the observation of ball metaphase." p. 304.

Taves goes on to say that:

"While Mohamed (1977) did not cite confirming studies of his earlier work in plants, there are at least four which are purported to confirm it." p. 304.

In one such study the investigators:

"...found that the percentage of chromosomal aberrations

in the roots approximately doubled with the 10^{-6} M (0.02 ppm) NaF solution and doubled again at 10^{-2} M." p. 304.

This study in addition to another which employed high fluoride concentration and work in two unpublished theses are cited by Taves as purported by others to confirm Mohamed's work in plants.

Taves cites other studies showing mutagenic effects of fluoride. He also includes some discussion on studies indicating an antimutagenic or protective effect of fluoride when known mutagenic substances are administered. Fluoride levels employed in such studies are generally high.

Gerdes et al (1971) studied the effect of atmospheric hydrogen fluoride (HF) on four genetic strains of Drosophila melanogaster. When exposed to atmospheres containing 0, 1.3, 2.9, 4.2 and 5.5 ppm HF for 6 weeks, there was observed a concentration-dependent decrease in survival of fruit flies from among all four strains. The 5.5 ppm level was lethal to all flies after only 3 days of exposure. At 1.3 ppm HF the percent survival relative to controls ranged, depending upon strain, from approximately 58% to 75%. The data in this study clearly show genetic strain differences in survival at the 1.3, 2.9 and 4.2 ppm HF. The authors advise that:

"Although this study was not designed to evaluate the reasons for differential responses of the populations tested, the data clearly show genetic relationships with ability to tolerate a specific pollutant." p. 115.

In a second study, Gerdes et al (1971a) investigated fecundity, hatchability and fertility of Drosophila melanogaster on exposure to atmospheres containing 0, 1.3 and 2.9 ppm HF. The effect of HF upon

fecundity of females hatched from eggs of parents exposed to HF concentrations studied. According to the authors of this study:

"The inverse relationship observed between the treatment duration of the parents and the fecundity of their female offspring suggests that exposure of Drosophila to low HF concentrations can cause genetic damage and that this genetic damage is accumulative as the exposure period is increased." p. 122.

This study by Gerdes et al is discussed in the National Research Council (1977) Review on the Effects of Fluoride.

The weight of evidence from these studies on mutagenic effects of fluoride indicates that the substance is mutagenic at low concentrations, i.e., at concentrations humans may be exposed to particularly in areas where high natural fluoride levels are found.

Deoxyribonucleic Acid (DNA) Studies

In important animal studies relating to mutagenesis and cancer, it has been shown that fluoride interferes with DNA excision-repair and DNA, RNA and protein synthesis.

Klein et al (1976) investigated the influence of sodium fluoride on DNA excision-repair capabilities of irradiated mouse spleen cell homogenates. In these studies mouse spleen was homogenized to disperse spleen cells in Hanks medium, and irradiated with ultraviolet or gamma radiation causing DNA damage. The capability of such cells to restore the damaged DNA via action of the cells' own DNA excision-repair enzymes was studied with and without sodium fluoride added to the homogenate. The authors indicate that DNA restoration can be monitored by the rate of incorporation of tritiated thymidine

(a DNA precursor) into DNA. These investigators reported definite fluoride-concentration-dependent inhibition of enzyme catalyzed DNA restoration. To be specific, sodium fluoride in the reaction medium at a concentration of 5×10^{-5} M (0.95 ppm fluoride) inhibited DNA excision-repair to the observed extent of about 50% relative to the control. A slight inhibitory effect was observed at the only lower concentration studied, 1×10^{-5} M (0.19 ppm fluoride). These adverse effects on DNA restoration were substantiated in this same paper by a second line of evidence where, based on diffusion velocity studies of DNA, sodium fluoride at the 5×10^{-5} M concentration was observed to reduce the lengthening of the DNA molecule during the period of restoration.

In an earlier paper Klein et al (1974) conducted in vivo experiments in which DNA excision-repair and DNA, RNA and protein syntheses were studied using Swiss mice. When the mice ingested fluoride from drinking water in a daily amount of 0.4 μ g fluoride/g body weight a slight increase in DNA repair was observed throughout the 12 weeks of study. (According to calculations by Armstrong (1977) based upon the volume of water consumed daily by such mice, the above figure of 0.4 μ g/g would arise from drinking water containing an estimated 2.5 ppm fluoride. Our calculations, however, yield an estimate of 4 ppm.) When the mice ingested 3.5 μ g fluoride/g body weight daily (estimated 21 ppm fluoride in drinking water by Armstrong (1977), but estimated by this author to be 35 ppm), there was observed a strong increase in DNA repair up to the 8th week of study. However, after the 10th week there was a nearly total inhibition of DNA repair. These influences

upon DNA restoration were confirmed by DNA sedimentation profiles. With regard to DNA and RNA synthesis, both levels of fluoride consumption resulted in concentration-related decreases (about 40% decrease or more in the case of those consuming 0.4 $\mu\text{g/g}$) after 10 weeks of exposure of the mice to this drinking water. With regard to protein synthesis, there were more modest concentration related decreases in protein synthesis after 8 weeks.

These studies have been characterized by Armstrong (1977) as interesting scientifically, but criticized as not related to human exposures from fluoridated water. With regard to the first experiment, Armstrong argues that the 0.95 ppm fluoride level in the homogenate was much higher than the level spleen cells would be exposed to within an individual consuming water containing 1 ppm fluoride. However, his own paper shows that in one community where the drinking water contained 2.5 ppm, residents' blood contained an average 0.16 ppm fluoride and in another community where 5.4 ppm was in the water, blood fluoride levels averaged 0.26 ppm. These values are extremely close to or exceed the 0.19 ppm fluoride level employed in the above study at which a small fluoride concentration dependent inhibitory effect on DNA excision-repair was observed. It should be noted that in contrast to information reported by Armstrong, Taves and Guy (1979) cite work showing somewhat lower plasma fluoride levels in blood bank samples taken within areas where drinking water fluoride levels were 2.1 and 5.6 ppm. However, these same investigators also cite studies in rats showing plasma levels nearly identical to those reported by Armstrong in humans at comparable fluoride levels in drinking water. Even if

human fluoride blood levels are more accurately described by Taves and Guy, the concerns over effects on DNA processes are not alleviated.

In the 1974 Klein et al paper, spleen cells studied from mice consuming water containing approximately 4.0 ppm fluoride exhibited enhanced DNA repair rates for the entire 12 weeks of study. These results thus affirm an effect of fluoride on the complex biochemical processes whereby defective DNA is repaired. This observed perturbation even though manifest as an increased repair rate may not be desirable. It is not known, for instance, that with chemically induced increased DNA excision-repair, the fidelity of repair is fully preserved. Any perturbation of this complex system must be viewed, a priori, as cause for concern. Cells taken from animals consuming water containing an estimated 35 ppm fluoride exhibited marked alterations in DNA repair ranging from a strong increase during the early weeks of exposure to nearly total inhibition of DNA repair at 10-12 weeks exposure. One might ask whether a decline in DNA repair rate would have been similarly observed in those animals consuming 4 ppm had the study been extended. These findings plus the inhibition of DNA, RNA and protein synthesis in mice after only 8-12 weeks of consumption of water containing 4 ppm fluoride must be viewed as cause for concern for those persons consuming water which contains 4 ppm fluoride, or even 1 ppm.

To pursue the matter further, while it is true that average blood fluoride levels of persons consuming water fluoridated at 1 ppm would not likely be within the very range of 0.19 to 0.95 ppm investigated by Klein et al (1976), there is still cause for concern

for the following reasons: In referring to average blood fluoride levels little consideration is given to individuals who, for one or more of a variety of reasons, may have fluoride levels well above the average. In addition, it can be assumed from this study that levels below 0.19 ppm would have an effect on DNA repair since the phenomenon was concentration dependent. Humans drinking fluoridated water are likely to be exposed for many years. Arguments such as these suggest that fluoride levels in the blood of a certain fraction of humans drinking fluoridated water may be within the range where perturbation of DNA repair is manifest and that at some point in time such perturbations may have serious consequence. Furthermore, out of 110 million people drinking fluoridated water, even a small fraction affected translates into a large number of persons.

There is yet another argument that should be presented. The phenomenon of DNA repair is important to every cell of the body. Though spleen cells would not be expected to be exposed to anything like 0.95 ppm fluoride in most persons consequent to ingestion of drinking water containing 1 ppm as Armstrong argues, what can be said, for example, of the level of exposure of stomach epithelial cells upon ingestion of fluoridated water? Granted, water entering the stomach would be diluted by the stomach contents, but the concentration of fluoride would be expected to be considerably higher than that of the blood. A further example could be the exposure of the various cells of the excretory system to urine containing high fluoride levels. Taves (1979a) provides a graph showing that fluoride levels in human

urine are very close to fluoride levels in the water consumed. For example, the graph shows a urine fluoride concentration of about 1.8 ppm when the drinking water contained 2.0 ppm, and about 0.9 ppm when the drinking water contained 1 ppm. Persons consuming water containing 4 ppm could be expected to have enhanced risk.

In a study by Tausch et al (1977), the English language summary indicates that DNA synthesis and DNA excision-repair were investigated in the lymphocytes of the peripheral blood of 6 patients undergoing fluoride treatment for osteoporosis. These patients received 11.3 mg fluoride daily (as sodium fluoride) in the first week and 22.6 mg fluoride during the subsequent period of treatment of 15 to 37 weeks. No significant effect was observed in 5 of these patients; however, one patient showed significantly inhibited DNA repair in lymphocytes up to the ninth week, an effect which disappeared during the subsequent period of treatment. This study involving a mere 6 patients must be viewed as incomplete and inconclusive, but inhibition of DNA repair for nine weeks duration in one of six patients is cause for concern, particularly when viewed in light of findings in the animal studies discussed.

It goes without saying that DNA excision-repair and DNA, RNA and protein synthesis are biochemical phenomena essential to the maintenance of the integrity of the living cell. Furthermore, perturbations in these phenomena and mutagenic effects are viewed by modern scientists as central to the cancer question. That this is true is supported by the following statements taken from the Occupational Safety and

Health Administration (1980), a newly released and widely publicized OSHA "cancer policy" statement. With reference to cancer under the topic Nature of the Disease and citing as the source of information statements by several outstanding cancer scientists, the following quotation is found:

"Much of this evidence supports the theory that cancer originates from cells which have been transformed, frequently by changes in or damage to the DNA or other genetic material. Although such damage to DNA may frequently be repaired, permanent cell transformation may result if the repair mechanisms are ineffective, or if the damage is repaired incorrectly. There is increasing evidence that at least some cancers may originate from a single transformed cell." p. 16.

Also cited in the same OSHA "cancer policy" statement are Schneiderman et al of the National Cancer Institute:

"First, cancer appears often to be a disease of DNA damage or misrepair, or incomplete repair and there is evidence that large numbers of molecules of an offending agent are not needed to cause DNA damage." p. 23.

By way of emphasizing the importance of all these considerations, suppose the one individual showing inhibited DNA repair in the Tausch et al study cited above had been exposed to a DNA damaging agent and damage to DNA occurred during the nine week interval that DNA excision repair was compromised, wouldn't this individual be expected to have enhanced vulnerability during that time to cancer or, for that matter, any other DNA-related malady?

The above animal studies indicate that consumption of fluoridated drinking water may lead to fluoride concentrations in the body very close to those concentrations where alterations in DNA excision repair and the other parameters discussed are beginning to be seen. There

appears to be virtually no margin of safety of the nature generally sought after or required for exposures to toxic substances. Since the studies cited here on DNA excision repair are very important, the work should be pursued in greater depth in order to assess reliability of the findings and to broaden the scope of understanding. For now the studies must be taken seriously.

More pharmacokinetic studies are needed to determine, for instance, blood fluoride levels as a function of rate of fluoride consumption and duration of exposure, remembering that unlike the studies in animals exposed for weeks, humans are being exposed for a lifetime. Individual drinking habits and quantities of fluoride consumed in foods, now being widely cooked and processed in fluoridated water, are quite variable and would be expected to play major roles in determining whether an individual's exposure exceeds or is below the level at which DNA excision repair might be affected. Individual levels of fluoride exposure also relate to the constancy of supply of fluoride in drinking water. Are we certain there are not pulses of high fluoride concentration in fluoridated or natural water supplies?

Further significant evidence of adverse influences of fluoride upon nucleic acids is provided by the work of Chang (1968) who studied the effects of sodium fluoride upon the development of root structures of corn seeds (Zea mays) grown in a water medium containing sodium fluoride at concentrations ranging from zero to 2×10^{-3} M. A fluoride concentration-dependent inhibition of root growth was observed.

At a sodium fluoride concentration of 2×10^{-3} M (38 ppm fluoride), the inhibition was approximately 75% as calculated from root mass developed relative to that of the control; at 1×10^{-3} M (19 ppm) inhibition was approximately 50% and at 5×10^{-4} M (9.5 ppm fluoride) inhibition was about 25%. Additional results from this study showed that fluoride at these same concentrations modified nucleotide ratios; and further than RNA structure was modified, incorporating relatively less cytosine and characterized by an increased ratio of cytosine to thymine. Such phenomena at the molecular level involving nucleic acids may provide an explanation for the mutagenic and carcinogenic effects attributed by some investigators to fluoride.

Cancer

Animal Studies.

Few animal studies have appeared in the literature assessing the possible carcinogenicity of fluoride. Those studies which have been undertaken are generally viewed as inconclusive. Nevertheless, some of these studies should be mentioned. As discussed by Schlatter (1977), Taylor in 1954 reported that 1 ppm fluoride administered in the drinking water of experimental mice was followed by an increase in the incidence of mammary tumors. Studies by Kanis and Schroeder in 1969, however, employing 10 ppm fluoride, did not confirm this finding in mice.

Taylor and Taylor (1965) studied the influence of sodium fluoride on the growth of mouse tumors inoculated into eggs and other mice. These investigators observed an increase in growth rate of such

tumors in these experimental systems. A level of sodium fluoride as low as 1 ppm in the drinking water of the experimental mice was observed to enhance the tumor growth rate. Criticisms of this study are that no dose response relationship was observed and that improper controls may have been used.

Herskowitz and Norton (1963), in studies involving two strains of Drosophila melanogaster, reported results showing that the presence of fluoride at 19 ppm (the lowest level studied) up to about 57 ppm in the larval nutrient medium resulted at the higher concentration level in a very high percentage of adult organisms developing melanotic tumors. A nearly linear dose response effect over the entire concentration range was observed with tumors occurring in about 90 percent of flies at the higher dosage. According to Taves (1979), citing Burton in 1977, melanotic tumors are like or resemble granulomas rather than neoplastic tumors. Such tumors would, however, raise a cancer concern.

Due to the lack of conclusive animal cancer data, the U. S. National Cancer Institute is initiating a much belated study on sodium fluoride in mice and rats. The study will involve a large number of animals of both sexes. Currently, prechronic studies are in progress which are designed to determine dosage levels and other factors prerequisite to a successful long term study. This long term study is not expected to begin until autumn of 1980 and will last 2-2½ years.

Human Studies

Taves (1979) cites the 1963 work of Okamura and Matsuhisa as indicating a correlation between stomach cancer and fluoride present in rice and "miso" of the diet. Fluoride levels in these foods is high. Taves also cites Hirayama in 1977 as reporting that stomach cancer rates in Japan were associated with intake of tea and fish, foods high in fluoride content.

Yiamouyiannis and Burk (1977) reported the results of an epidemiological study covering cancer mortality in the ten largest fluoridated cities in the United States as compared with ten of the largest non-fluoridated United States cities. These investigators reported the finding that between 1952 and 1969 there was no statistically significant increase in cancer death rate in the 0-24 and 25-44 year age groups. However, for the 45-64 age group a statistically significant increase ($p < .02$) in cancer death rate of 15/100,000 population was found in the fluoridated cities. Similarly, in the 65+ age group a statistically significant ($p < .05$) increase in cancer death rate of 35/100,000 population was observed. These investigators noted that such changes could not be attributed to race or sex compositions of the populations under study. This particular study was the culmination of earlier studies of Yiamouyiannis and Burk appearing in the Congressional Record (Delany (1975, 1975a)).

In response to this earlier work appearing in the Congressional Record, studies of similar data were conducted by Hoover et al (1976) of the U. S. National Cancer Institute, Doll and Kinlen (1977) of the Uni-

versity of Oxford and Oldham and Newell (1977) of the Royal Statistical Society. These studies did not show a significant increase in cancer incidence or mortality in the fluoridated cities. The Hoover study did show a statistically significant increase in stomach cancer in the male population from among the several cancer sites under study. This, however, appears to have been dismissed as a chance variation. In commenting on this aspect of the Hoover study, Taves (1979) says:

"A linkage between stomach cancer with fluoride would not be unreasonable because fluoride exists primarily as hydrofluoric acid, a highly penetrating and irritating chemical, in the acid stomach." p. 311.

It should be noted also that data in the epidemiological study by Erickson (1978) indicated an 8.8% excess death rate of cancer of the digestive system in fluoridated versus non-fluoridated cities, even after the raw data was corrected for age, race and sex differences within the populations. After yet additional corrective parameters were applied, this difference in digestive system cancer rate disappeared; however, the additional corrective factors employed are questionable.

The above studies are claimed to refute the original findings of Yiamouyiannis and Burk appearing in the Congressional Record, which had been based on crude mortality data not corrected for age, sex or racial makeup of the populations under study. However, Yiamouyiannis and Burk (1977) then published the findings presented above which took into account these variables and which showed increases in cancer mortality for the 45-64 and 65+ age groups. An elucidation of the reasons for the difference in the findings among these inves-

tigators came out forcefully in both the National Cancer Program (1977) and the proceedings of a November, 1978 hearing in the Court of Common Pleas of Allegheny County, Pennsylvania, Judge John P. Flaherty presiding. In the latter instance, plaintiffs sought action to halt fluoridation of water supplies in the county. Several leading authorities on both sides of the fluoridation issue testified on many subjects relating to the health effects of fluoride during this court proceeding. To be brief, the result of this court case was that Judge Flaherty (1978) entered an injunction against the fluoridation of the public water supply of the area in question:

"In short, this court was compellingly convinced of the evidence in favor of plaintiffs."

Flaherty (1979) in commenting on the ruling in his court indicated:

"In my view, the evidence is quite convincing that the addition of sodium fluoride to the public water supply at one part per million is extremely deleterious to the human body, and, a review of the evidence will disclose that there was no convincing evidence to the contrary."

From a review of the evidence presented in this case, (Winner et al (1978) counsel for the plaintiff), it became evident that the Hoover et al (1976), Doll and Kinlen (1977) and Oldham and Newell (1977) studies had all included a common error which explained part of the discrepancy between these studies and that of Yiamouyiannis and Burk (1977), and that the remainder of the differences could be explained in terms of differences in concepts used in computing the results.

A lengthy and complex discussion would be required at this point to compare the methods used by Yiamouyiannis and Burk and the other investigators. Having reviewed all four of the above studies plus others

(Taves (1977) and Erickson (1978)), as well as some of the testimony presented in the National Cancer Program (1977), Winner et al (1978) and the Water Authority's summary (1978), it appears that Yiamouyiannis and Burk have correctly approached the problem and that their findings stand unsuccessfully refuted. The defense made by Yiamouyiannis and Burk of their own work in these places of debate is intellectually persuasive as is their criticism of the calculations and methods used by the other investigators. The arguments presented by those who oppose the Yiamouyiannis and Burk study, in trying to explain away a correlation between fluoridation and increased cancer mortality, leveled principally at the claimed unorthodox approach taken by Yiamouyiannis and Burk, are simply not convincing. Though the correlation reported by Yiamouyiannis and Burk is, in terms of percentages, a relatively small one, i.e., 4-5% excess cancer deaths, (this is by no means small in terms of the absolute numbers of excess cancer deaths) and likely would tax the capabilities of any method of epidemiology at detection, where the health of many individuals out of 110 million Americans is potentially concerned arguments disproving the finding must be extremely persuasive if our concerns are to be allayed. This condition has not been met. It must be emphasized, however, that the authors of those epidemiological studies which do not show the correlation between fluoridation and cancer maintain the position that their findings are accurate.

The author of this report must confess to not being a statistician or epidemiologist, but much of the reasoning employed in these studies,

particularly in the areas where there is controversy, is of a nature which can be comprehended and evaluated by scientists in general, and also by lay persons. Copies of the publications containing the methods and reasoning employed by the various investigators are present in the Bureau of Toxic Substances Information. Interested parties are encouraged to review the studies and relevant testimony cited here in order that each might reach his own interpretation of the conclusions drawn from the data.

The correlation found between fluoridation and increases in cancer mortality does not prove that fluoridation is a cause of cancer, as some other yet undefined parameter could explain away the correlation. However, until some alternative reliable explanation for the differences noted between the fluoridated and non-fluoridated cities can be offered, these findings must be viewed with respect.

Dental Caries Reduction

It is not the purpose of this report to review evidence on the effectiveness of fluoride in preventing dental caries. Such an in-depth study, however, should be undertaken for the benefit of the Health Department. Many studies have been cited showing the dental benefits of fluoride. Adler (1970) in reviewing the subject of fluoride and dental health, cites studies by Dean indicating the clear finding of dental caries reduction as the fluoride content of drinking water increases, up to about 1 ppm. Little further benefit was observed at levels beyond 1 ppm. Adler cites additional studies showing not only improved dental caries experience with fluoridation but decreased

loss of teeth as well. According to this review, dental caries may be reduced 50-60%. Fluoride appears to be most effective in dental caries reduction when administered during childhood up to about the 12th year of age.

The National Institutes of Health, Division of Dental Health (1971), has summarized several studies showing a reduction of as much as 2/3 in dental caries by fluoridation. These studies also reveal decreased tooth loss with fluoridation.

Thus, much evidence affirms these positive dental effects with fluoridation. In view of these findings, it would be unconscionable to deny such benefits to the public on the basis of false claims of harm attributed to fluoride. These weighty considerations demand the best efforts on the part of health scientists to determine the biological effects of fluoride.

Summary

A number of studies relating to the health effects of fluoride have been presented in this report. On the question of dental fluorosis or mottling of teeth it appears that 2 ppm fluoride in drinking water represents a level above which significant mottling would be expected. It is suggested that in those population areas where drinking water contains more than 2 ppm fluoride, dental surveys be conducted to determine whether in fact dental fluorosis is a problem.

Where the skeletal system is concerned, the weight of evidence indicates that fluoride in drinking water at concentrations up to 4 ppm

would not be expected to have harmful effects on the skeleton. Above this level findings vary; however, in the range 4-8 ppm certain fractions of exposed populations exhibit adverse skeletal effects. Levels above 10 ppm ingested over periods of 10-20 years is associated with the development of skeletal fluorosis, a painful and debilitating condition.

Beyond the dental and skeletal effects of fluoride a distinct body of information exists indicating that fluoride exerts adverse metabolic effects at low levels on several life forms including man.

Furthermore, these metabolic effects carry implications for and support those studies showing adverse health effects in man. For example, the Yiamouyiannis and Burk study reveals increased cancer mortality in fluoridated cities. Though this study has been challenged by many other studies, the low percentage increase (4-5%) in cancer mortality (actually representing a large number of individual persons) is consistent with what would be expected from evidence that fluoride at low levels inhibits DNA excision-repair, inhibits DNA, RNA and protein synthesis, exhibits mutagenic type effects in several studies, modifies plant RNA structure accompanied by alterations of cytosine to thymine base ratios, induces melanotic tumors in Drosophila, has given evidence of causing and promoting tumor growth in rats and has been implicated as a cause of stomach cancer in man. Although this body of evidence does not definitively establish that fluoride is a cause of increased cancer mortality, the evidence is sufficiently persuasive that health officials should be concerned about the ingestion of fluoridated water at the 1 ppm level, and certainly above this level.

Enhancing the concern would be the experimental evidence that fluoride in drinking water at the 5 ppm level and lower fosters cytochemical changes in the kidney. Furthermore, where the kidney is concerned persons with impaired kidney function may suffer from acute fluoride toxicity when consuming water containing as little as 2 ppm fluoride.

The finding of Hirata in Japan of a decrease in white blood corpuscles and neutrophils in children of prepuberty age, which was correlateable with the extent of dental mottling observed where the drinking water contained 1-5 ppm fluoride, is a serious and important finding.

There is the added question of Down's syndrome to be reckoned with. Work has been cited showing a dose related association between fluoride and the incidence of Down's syndrome where fluoride levels in the drinking water ranged from 0.1 to 2.6 ppm. Though this work has been seriously criticized, the fact remains that no study satisfactorily refutes the findings. The possibility of a fluoride-related increased incidence of Down's syndrome remains.

Additional important health effects not discussed previously in this report because of difficulty of evaluation are the reports of allergies and other adverse conditions observed by a physician in his private medical practice (Waldbott et al (1978)). These are important health matters and this volume should be taken into consideration by health officials who are reviewing fluoride. In reference to the use of fluoride tablets, where the intended combined daily dose of fluoride from drinking water and from the tablets is about 1 mg, the Physicians

Desk Reference (1979) indicates fluoride may cause a variety of symptoms such as skin eruptions, eczema, gastric distress, headache, weakness, etc. in hypersensitive individuals. Out of 110 million persons consuming water containing fluoride, there may be many experiencing such symptoms who have no idea that fluoride in the drinking water may be the cause.

The weight of all the studies leads this writer to the opinion that fluoride should be reduced in those drinking waters of the State where it is naturally high, particularly if there is evidence of dental fluorosis.

Where fluoridation itself is concerned, it must be recognized that the practice is widely endorsed and implemented in the United States. The list of endorsements by professional associations is so lengthy that it would take excessive space to reproduce here. A few notable examples are: American Association for the Advancement of Science, American Dental Association, American Medical Association, American Pharmaceutical Association, American Public Health Association, etc. It should be noted that late in 1979 the American Public Health Association (1980) adopted a resolution urging national health organizations to hold annual meetings or conventions only in fluoridated communities, recognizing as appropriate such economic sanctions in promoting fluoridation. These many endorsements of fluoridation attest to the magnitude of confidence such organizations have that fluoridation of drinking water is a wholesome practice.

Nevertheless, numerous communities in the United States have not accepted fluoridation in view of the adverse health effects cited against this practice. These acts or decisions attest to the magnitude of concern of those who on the other hand believe fluoridation may be dangerous or who are convinced that sufficient doubt as to its safety remains.

With regard to fluoridation, this writer is of the opinion that the evidence of adverse health effects is of such magnitude and human beings so varied in their individual constitution, state of health at any moment, eating and drinking habits, etc., that it is inappropriate to say that fluoridation is a totally healthful and safe practice for all. Widespread exposure to fluoride coupled with an inadequate data base substantiating it to be safe is a cause of great concern. The public consumes fluoride from drinking water, tooth paste, mouth washes, etc. with little or no advice as to how much fluoride is enough or too much. The evidence as cited herein indicates some adverse health or metabolic effects right at or very close to the 1 ppm level, with no margin of safety respecting such effects established of the nature generally sought for toxic substances. It is possible that many individuals out of the large number consuming fluoridated water are suffering in varying degrees health detriment attributable to this recognized toxic substance.

In summarizing complex information, there is the risk of being considered incomplete. Nevertheless, this report represents an effort to bring to the attention of Virginia State Health Department per-

sonnel information on the controversy that continues. The evaluation of fluoridation and the health effects of fluoride is incomplete and should be ongoing; hence, the Bureau of Toxic Substances Information will continue to review the fluoride literature.

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