Safety factors in water fluoridation based on the toxicology of fluorides

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Introduction

Before considering the various toxic effects of fluorides in their relation to water fluoridation, four preliminary points will be made.

First, the discussions will be limited to brief descriptions of six major toxic effects, each of which has been studied in sufficient detail to permit quantitative comparisons of the doses required to produce the effect with the amount recommended for the public health measure, water fluoridation, which utilizes small concentrations of fluoride to reduce dental decay. That is not to say that other fluoride effects have not been investigated from the point of view of establishing the safety of water fluoridation, but a major interest of the toxicologist lies in the margins of safety, and these estimations are based on numerical comparisons of amounts or concentrations of fluoride.

Table 1. *Notes on fluoride metabolism*

1. *Fluoride absorption.* (a) Soluble fluorides are rapidly absorbed from the gastro-intestinal tract (some from the stomach). (b) Insoluble fluorides when ingested are slowly and incompletely absorbed. Complexing elements (e.g. calcium, aluminium) retard absorption.

2. *Fluoride distribution.* (a) Fluoride absorbed (only as the fluoride ion) is rapidly distributed throughout the extracellular body water in a pattern essentially similar to that of chloride. (b) The principal distribution pattern is simple: part goes to bone, the remainder is soon excreted through the kidney. (c) The fluoride concentrations in tissues other than bone and kidney (e.g. saliva, milk and foetal blood) tend to follow blood concentrations but at a lower level.

3. *Fluoride deposition.* (a) Fluoride is a bone seeker: in an unexposed individual up to half an absorbed dose is rapidly deposited. (b) With prolonged exposure a steady state is established with no net increment in fluoride content. (c) The larger the daily fluoride intake, the higher, but not proportionately, the ultimate bone concentration. (d) The higher the drinking water concentration, the greater the fluoride content of tooth tissues. Surface enamel is rich in fluoride and may also fix some fluoride in the immediate posteruptive period. Dentine and cementum are similar to bone. (e) Fluoride enters bone and tooth mineral by exchange with hydroxyl ions in the hydroxyapatite lattice. (f) Topical applications of concentrated fluoride solutions produce in addition superficial and temporary calcium fluoride deposits. (g) No soft tissue stores fluoride. (h) Skeletal fluoride is slowly mobilized by haversian reworking.

4. *Fluoride excretion.* (a) Fluorides are rapidly excreted, principally in the urine, e.g. in 3 h, in man, $\frac{1}{7}$–$\frac{1}{4}$ of an oral dose of a few mg. (b) The renal mechanism depends on a less efficient (92%) resorption than is usual for chlorides (>99%). (c) The higher the intake of soluble fluoride, the higher the urinary concentration. (d) Faecal excretion accounts for a small fraction of the amount absorbed. (e) Excretion in sweat also accounts for a small fraction (more during excessive sweating).

Second, a knowledge of the fate of fluoride in the body contributes to an understanding of the physiological and pathological effects. Since a detailed discussion of fluoride metabolism cannot be presented at this time, attention is directed to the notes in Table 1. One major concept of fluoride distribution should be stated before any general discussion of fluoride toxicology is begun. The distribution within the body of an ingested dose of fluoride is largely dependent upon the degree and duration of the previous exposure to fluoride. From a recent resumé (Hodge, 1961), a few details of these relations can be drawn.

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(1) In an unexposed animal, fluoride distribution is characteristically rapid and simple. After 3 h, for example, half a small dose (a few mg) will have been deposited in the bone, about a quarter will have been excreted in the urine, and the balance will be found in the blood (trace), the kidneys and other soft tissues. After 24 h, nearly half the fluoride dose is still in the bone and the rest will have been lost from the body in the urine.

(2) In an individual exposed daily to a small amount of fluoride for a long time, a steady state has been established: there is no net increment of fluoride to the skeleton. In man, because of the osteoblastic–osteoclastic reworking of the skeleton, a fraction of the daily intake, perhaps 30 or 40%, is built into the bone; the balance is lost in the urine. Simultaneously, osteoclasis releases as much fluoride as is fixed by osteoblastic renewal.

(3) In assessing the effects of fluoride administration, the cumulative nature of fluoride must be kept in mind. It is not enough to state the doses of fluoride: the duration of repeated dosing may be a controlling factor in the kind or intensity of effect.

(4) In expressing quantitative factors of safety in water fluoridation, the assumption, based on the work of Longwell (1957) and others, is made that the average adult drinks about 1·5 l. water daily, therefrom ingesting 1·5 mg fluoride which, together with 1·3–1·8 mg fluoride consumed especially in tea and in part in solid food, totals 2 or 3 mg fluoride. For the average child, whose daily water consumption is less than 1 l., the probable intake is about 1 mg fluoride. When appropriate, safety factors are expressed on the basis of the latter amount.

Acute lethal dose: *factor of safety* 2500–5000 *times*

A mass poisoning in the Oregon State Hospital (Lidbeck, Hill & Beeman, 1943) occurred when 17 lb of sodium fluoride were 'unwittingly' mixed into a 10 gal batch of scrambled eggs and served throughout the hospital: 263 patients were poisoned; 47 died. There were complaints immediately of salty or soapy sensations or numbness in the mouth; nausea, vomiting, diarrhoea and abdominal cramps promptly developed. Severely poisoned individuals soon collapsed exhibiting pallor, weak pulse, shallow respiration and cyanosis. Death, in most instances, ensued 2–4 h after the ingestion (emphasizing the rapidity of the absorption of fluoride). The rapidity of excretion also is emphasized by the survival of nearly all who lived for more than 4 h. In fact, Black, Kleiner & Bolker (1949) administered intravenously what must have been nearly half a lethal dose daily for 9 days to a patient without observing any toxic reaction. Over 600 deaths in the USA have been attributed to fluoride poisoning since 1933; the 'certainly lethal dose' for the adult (2500–5000 mg fluoride, 5–10 g sodium fluoride) has been estimated from the frequently fragmentary data in these and other records on amounts ingested and retained.

Kidney injury: *factor of safety* 100 *times*

Repeated large doses of fluorides in several species of animal ultimately induce

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dilation of some of the renal tubules, characteristically a dilation of the thin section; changes in kidney function, e.g. increased urinary volume and decreased specific gravity, have also been observed. In a few of a group of rats treated for 6 months, these histological changes occurred when the drinking water contained 100 p.p.m. but none occurred when it contained 50 p.p.m., as my colleagues and I have shown (Taylor, Gardner, Scott, Maynard, Downs, Smith & Hodge, 1961). From a large body of animal data the minimal fluoride concentration in the drinking water to give kidney injury on repeated administration is estimated at 100 p.p.m. (Hodge & Smith, 1963). Serious kidney injury or disease does not interfere with fluoride excretion, e.g. in rabbits given near-fatal doses of uranium (a kidney poison), in rats poisoned with fluoride, in elderly patients and in children suffering from kidney diseases (Hodge & Smith, 1954). Major increases in kidney disease or deaths have not been reported from areas where the drinking water is naturally fluoridated; these health and mortality statistics are too gross to detect morbidity limited to a few persons. Unevaluated reports of pathological changes in residents in India who have drunk water containing from 2·5 to 11 p.p.m. for 40–60 years need further investigation. At present, evidence of the absence of kidney effects in human populations can be drawn from three sources: (1) clinical opinions of physicians in areas of naturally fluoridated water; (2) limited observations, e.g. the normal urinary albumin and glucose levels of Texas residents whose drinking water contained 8 p.p.m., together with (3) the reliable demonstration of normal kidney function in the 10-year study of children in Newburgh, New York, after water fluoridation had been introduced. Controlled, large-scale epidemiological studies have not yet been employed.

Thyroid injury: factor of safety 50 times

Because the halogen, iodine, is concentrated in the thyroid, the question of fluoride concentration therein was raised long ago. It was easy to imagine that if fluoride were also concentrated it might be antagonistic to the normal utilization of iodine. These fears were groundless. Fluoride is not concentrated in the thyroid. Studies with radioactive fluoride such as my colleagues and I have made (Hein, Bonner, Brudevold, Smith & Hodge, 1956) show that the thyroid level follows but remains slightly below that of the blood. Furthermore, no relation exists between goitre and fluoride in the drinking water. Goitre occurs where the water contains little or no fluoride. Elevated fluoride concentrations in the drinking water do not on the one hand lead to increased incidence of goitre or on the other to any lessening of the usefulness of iodine in goitre prevention.

Histological changes and functional changes have been shown in a large number of experimental animals given very large doses of fluoride; for example, mild atrophy occurs in the thyroids of rats given daily 50 mg/kg body-weight. Lower concentrations (the limit has been estimated at 50 p.p.m. in the diet or drinking water based on a large body of data) apparently are ineffective in influencing either thyroid structure or function (Hodge & Smith, 1954).

Growth retardation: factor of safety 40 times

From experiments in which large numbers, and many species, of animals have been fed on diets containing various concentrations of fluoride for varying lengths of time, the conclusion can clearly be drawn that for most species 100 p.p.m. in the diet failed to retard growth. The cow is apparently the most susceptible species. For the cow going through periodic cycles of gestation and lactation, it has been well documented that 40 p.p.m. fluoride produce a gradual loss of weight and of good health (Hodge & Smith, 1963). Growth data from Newburgh–Kingston, in New York, show normal development in the children drinking fluoridated water. There are no proven instances of human growth retardation by fluoride (at any concentration). The only purported instance, a possible growth stunting of Japanese children living in a small village on a volcanic mountainside, cannot be evaluated in the absence of data on the nutritional status, hereditary background and health history (Baba & Shunko, 1950).

Reproduction

Because public attention has been focused recently on the tragic thalidomide effects, brief mention will be made of the many observations of reproductive performance in a number of species ingesting fluoride (Hodge & Smith, 1963). No teratogenic effects have been detected. When diets contained large amounts of fluoride, delayed oestrus, failures to conceive repeatedly, decreased birth weights and lowered viability of the offspring can be detected. The lowest fluoride level at which such interference with reproduction has been reported is 70 p.p.m. when given for a protracted period to cows.

Crippling fluorosis : factor of safety 20–80 or more times

This industrial disease identified by Roholm (1937) is described in his classic monograph *Fluorine Intoxication*. Danish workmen in the dusty cryolite industry became crippled and could no longer perform simple physical tasks. Exposures to 20 or 80 or more mg F/day for 10–20 years were responsible for the development of osteosclerosis, exostoses, and calcification of the ligaments. The consequent fixation of the spinal column, the 'poker back', was crippling. The toxic effects of fluoride on long-continued administration in these relatively large amounts are characteristically limited to the skeleton. A crippling disorder similar in most details develops in animals.

Histologically, bone formation occurs from the periosteum and from the endosteum with consequent thickening of the long bones and radiographic osteosclerosis. Osteoporotic loci develop in the pre-existing compact bone where osteoblastic activity has been inhibited. Observations of radiographic osteosclerosis in man show with considerable reliability that drinking water containing 8 p.p.m. F will ultimately produce osteosclerotic changes in about one of ten individuals. The validity of this critical concentration is reinforced by the industrial experience which has shown that osteosclerosis never develops if the urine contains less than 5 mg F/l. (Hodge & Smith, 1954).

Attempts to find a role of fluoride in bone diseases, such as rickets, rheumatoid spondylitis and arthritis, have to date been unsuccessful. Normal fluoride concentrations have been found in these diseased bones (Steinberg, Gardner, Smith & Hodge, 1955, 1958). Crippling fluorosis has been reported from India and China in patients who apparently had ingested little fluoride. Unfortunately, fluoride balance data in these individuals were not obtained. Fragmentary data on the urinary fluoride excretion, 13–41 p.p.m., indicate that the fluoride intake may well have been within the limits known to produce osteosclerosis or crippling fluorosis in Western industry. It may be, however, that populations living on inadequate diets respond to a given fluoride intake with more severe signs of fluorosis than occur in well-nourished populations (Hodge & Smith, 1963). Rats, for example, maintained on low-calcium diets, showed increased susceptibility to acute fluoride effects.

Many interesting questions about the effects of fluoride on bone have been raised, for example whether small doses of fluoride are beneficial to the health of the skeleton and retard the typical osteoporosis or osteomalacia in elderly patients. Annual radiographs of wrists and knees of children in Newburgh and Kingston, New York, read 'blind' by a competent radiologist, demonstrated normal skeletal age and development of those drinking fluoridated water. The higher incidence of cortical defects in the Newburgh children's long bones, although these changes are considered by the specialist in children's roentgenology to be 'normal' variants (Coffey, 1955), deserves additional study.

Mottled enamel: factor of safety 2–8 or more times

An interference with enamel development producing hypoplastic (or more accurately metaplastic) changes in the peripheral portion of the enamel was first recognized as a fluoride effect in 1931, independently by chemical techniques and by animal feeding studies. In the 1930s, the degrees of severity of change in the enamel surface were defined and the relation between the severity and the fluoride content in the community water supply was discovered. The absence of unaesthetic mottling in communities where the drinking water contains about 1 p.p.m. F and the gradual increase in the number of children so affected as the fluoride concentration increases from 2 to 8 p.p.m. is known quantitatively with a reliability rare in biological data (Dean, Arnold & Elvove, 1942). The margin of safety is small but is established firmly (Hodge, 1950).

The term 'mottling' suggests disfigurement; this is an unfortunate connotation, because (1) enamel hypoplasia of a very mild sort occurs spontaneously in the teeth of many who drink water which is virtually free from fluoride, and (2) the degree of mottling which develops when drinking water contains about 1 p.p.m. is so insignificant that only expert dental examiners can recognize it; i.e. the teeth appear normal to the inexpert eye. Mottled enamel arises as a result of interference with the normal function of the ameloblast, the cell which lays down the enamel rod in the forming tooth. This non-specific injury can be produced by vitamin deficiency, mechanical trauma or systematic illness as well as by fluoride. Mottling obviously can only be produced during the time that the enamel is forming, before the tooth

erupts. No mottling of the enamel can be produced in erupted teeth, regardless of the fluoride intake.

The regularity of the increase in the community index of severity of enamel mottling with increasing concentration of fluoride (above 1 p.p.m.) in the drinking water might suggest that there is a uniformity among individuals in this response. It is not so. In a given population, some children will have normal tooth surfaces, others may exhibit mild, moderate or severe mottling; the relative numbers in each category depend on the fluoride concentration in the water. The higher the concentration, the greater the proportion of children exhibiting more severe degrees of mottling. The factors controlling this distribution are unknown. It may be postulated that the total amount of water consumed, the quality of the diet, the state of health of the child and possibly hereditary and other factors are involved.

Public health applications: water fluoridation

No reasonable doubt exists that populations drinking water containing 1 p.p.m. F enjoy considerable benefit in lessened dental decay. In such populations, although skeletal storage may continue, as we and others (e.g. Hodge & Smith, 1954) have shown, during a major part of the life of the individuals, both in the bones and to a lesser extent in the teeth, steady states are ultimately established in which no further net increment in the fluoride content occurs (Jackson & Weidmann, 1958). These concentrations of fluoride are not associated with any detectable alterations in the structure or the physiological functions of the tissues, except for the reduction in dental caries.

What can be said of the general health of those who drink fluoridated water? A persuasive guarantee of the safety of water fluoridation lies in the fact that over 3 million people in the USA alone have for their lifetime drunk from naturally fluoridated water supplies containing 1 p.p.m. F or more, and over 7 million from supplies containing 0·7 p.p.m. F or more. Although a large-scale epidemiological study is lacking, physicians and public health experts who live in these areas have not become aware of disorders peculiar to these localities or of diseases more frequent, more severe, or different than elsewhere. No ill effect of drinking fluoridated water at 1 p.p.m. is known.

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