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Title: **Fluorine – Human Health Risks**

Author: Fiona M. Fordyce
British Geological Survey
West Mains Road
Edinburgh
EH9 3LA
UK
fmf@bgs.ac.uk

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Fluorine (fluoride) is beneficial to human health in low concentration but toxic in excess. One of the main exposure routes is via drinking water. It is unproven whether fluoride is essential for health but numerous studies have demonstrated that low concentrations in drinking water (0-0.5 mg L^{-1}) are associated with increased dental caries (tooth decay) rates whereas contents of 0.5-1.5 mg L^{-1} are protective against the disease. As a result, fluoride is widely used in dental products and water fluoridation programs have been implemented in many countries. However, exposure to higher concentrations via drinking water (> 1.5 mg L^{-1}), some teas and fluoride-contaminated salt and the burning of high-fluoride fuels can cause deformities of the hard tissues, namely dental and skeletal fluorosis. Dental fluorosis is an irregular calcification disorder of the enamel-forming process during childhood leading to pitted, stained and eroded teeth. In contrast, skeletal fluorosis is a crippling disease caused by over-mineralization of the bones and joints as a result of longer term exposure to high fluoride intakes. It is estimated that these diseases affect over 70 million people globally, limiting their ability to work and support their families. Hence the need for better understanding of environmental exposure to help mitigate these health outcomes.

Chapter:

Introduction

Fluorine is a naturally occurring chemical element, which exists in the rocks, soils, waters, air, plants and animals on Earth. It is the 13th most abundant in the Earth's crust and the most electronegative and reactive of all the elements. As a result, elemental fluorine does not occur in nature but is found as the fluoride ionic form and in minerals. This article focuses on the health impacts of inorganic fluorides. Human fluoride exposure can occur via inhalation, dermal contact or more commonly through ingestion of food, beverages, dental products and drinking water. The term fluorosis (fluoride toxicity) was coined by Christiani and Gautier in 1925 to describe the impacts on vegetation of emissions from a Swiss aluminum smelter. In the early 1930s, human skeletal fluorosis was reported in France and Denmark related to exposure in mineral processing and cryolite (Na_3AlF_6) mines respectively. Skeletal fluorosis was recognized as an endemic disease in India in the late 1930s and has since been reported in many parts of the world. The disease, which can cause crippling bone deformities, is commonly related to high fluoride intakes from drinking water, tea, foodstuffs and inhalation from coal-based fuels. Recent estimates suggest that 1.7 million people in China and 1 million people in India suffer from the disease (WHO, 2006). The detrimental health effects of fluoride in humans were also noted during the late 1800s and early 1900s in populations in Mexico, Italy and the USA where black teeth and eroded dental enamel were recorded. However, it was studies by Smith and co-workers in the 1930s that established fluoride in drinking water as the cause of this disease known as dental fluorosis. Dental fluorosis has since been reported from all around the globe and latest estimates suggest that it may affect 70 million people (WHO, 2006). Subsequent epidemiological investigations by Dean and colleagues in the USA during the 1930s and 1940s confirmed the relationships between the severity of dental fluorosis and increasing fluoride contents in drinking water. However, this work also demonstrated the beneficial effect of the element in the prevention of dental caries (decayed or missing teeth). As a result fluoridation programs have been implemented in many countries and millions of people around the world are familiar with fluoride as a constituent of dental-care products. Today the benefaction of water (and other) fluoridation programs is increasingly questioned in the context of better oral hygiene in many parts of the world, whereas concerns remain about the detrimental impacts of the element on the millions of people exposed to high fluoride intakes, particularly in developing countries. Comprehensive reviews of the health impacts of fluoride have been carried out recently by the World Health Organization (WHO) and Agency for Toxic Substances and Disease Registry (ATSDR) (see the section 'Further reading'); a summary of the main issues is presented in this article.

Fluoride Health Effects

Like several other naturally occurring chemical elements, fluoride has both beneficial and detrimental effects on human health depending on the levels of exposure.

Once absorbed in the human body, the majority of fluoride (approximately 60-80 %) is retained in the skeleton and the range of fluoride content of human bones is typically 300-7000 mg kg^{-1} dry tissue depending on exposure. In contrast, fluoride levels in blood are normally very low typically ranging from 0.04 mg L^{-1} in normal circumstances to 0.5-0.8 mg L^{-1} in fluorosed populations. The retention of fluoride in bones versus excretion via the kidneys (and partly the skin) plays the most important role in the homeostatic mechanism responsible for maintaining the fluoride concentration in blood. A certain proportion of fluoride (data from different studies estimate 15-50 %) remains in an ionic state and the rest forms albumin bonds with calcium acting as a bond mediator. The lowest fluoride concentrations are found in body soft tissues, which generally contain 0.5-1.0 mg kg^{-1}. However, concentrations of 3-50 mg kg^{-1} are not uncommon in epidermal tissues. Therefore, the main fluoride health issues are associated with bones and teeth.

Beneficial Health Effects

Scientists are still uncertain whether fluoride is essential to human health but the element has been used successfully to combat both dental and skeletal health effects.

Fluoride in Dental Caries Prevention

Dental caries is one of the most widespread diseases affecting humankind. It is estimated that in developed countries, dental caries prevalence is currently 95-98 % and these rates are rising in all cultures around the world where fluoridation/ oral-hygiene schemes have not been introduced. Caries is the most common cause of tooth loss, inhibited mastication and poor digestion. Following the work of Dean in the 1940s, numerous studies carried out in the USA and Europe demonstrated a link between improved dental health and the introduction of fluoridated drinking water to local communities. Caries prevalence where the water fluoride content was 1 mg L^{-1} or more was found to be almost half that of communities where drinking water contained 0.1-0.3 mg L^{-1} and many countries adopted successful water fluoridation programs. Indeed this was one of the major public health initiatives of the 20^{th} century. An array of fluoridated dental products followed including toothpastes, mouth rinses, gels, varnishes, solutions and tablets as well as fluoridated milk and salt the in some countries. Studies have demonstrated that fluoride is most beneficial when constantly present in small quantities in saliva and dental plaque. Hence, fluoridated water, toothpaste and salt programs are considered now to be the most efficacious and easiest to implement in public health, particularly for poorer communities.

In more recent years, as oral hygiene has improved in the world, the difference in caries prevalence between fluoridated and non-fluoridated drinking water populations has significantly decreased. This is particularly true in developed countries due to

intake of fluoride from other sources, primarily dental products. The WHO estimate that whereas 210 million people have access to drinking water with optimal levels of fluoride for caries prevention, more than double that number, that is 500 million people are exposed to the element via the use of fluoridated toothpaste. As a result, in parts of the world with good oral hygiene, the need for and added benefits from mass water/salt fluoridation programs are increasingly called into question.

The mechanisms of dental benefaction of fluoride are thought to be several-fold. Firstly, teeth are formed from the calcium mineral hydroxylapatite. Fluoride is a powerful calcium-seeking element, hence, during the pre-eruptive stage (i.e. during tooth formation in children up to 12 years old) ingested fluoride is thought to accelerate the mineralization process. It can also enter the mineral lattice forming fluorapatite, which is stronger (less soluble) than hydroxylapatite but more brittle. Secondly, fluoride acts as an anti-bacterial agent in the mouth helping to minimize acid-attack on teeth. More recent evidence suggests that the presence of fluoride in saliva and dental plaque also enhances remineralization at the surface of erupted teeth and this is thought now to be the primary caries prevention mechanism

Osteoporosis Treatment

Fluoride has been used in the treatment of age-related osteoporosis in high doses of 20-30 mg day^{-1} sodium fluoride (NaF) and monofluorophosphate (Na_2FPO_3) for the last 40 years. The success of the treatments depends not only on the dose but on the nutritional status, absorption capacity and renal threshold of the individual; hence the element is often given in conjunction with calcium and Vitamin D. These treatments have been shown to increase trabecular (spongy) bone density but not cortical (compact) bone density and protect against vertebral fractures. However, studies exploring fluoride-treated osteoporosis patients versus control groups and populations exposed to high versus low fluoride drinking waters give conflicting evidence of the benefits in the prevention of other fractures, particularly of the hip. Some results demonstrate a protective role and others an increase in fracture rates. Side effects of treatment can include gastrointestinal pains; microfractures of the feet and calcium deficiency.

Detrimental Health Effects

Fluoride is a known toxin and acute and high-dose exposure to the element (particularly via inhalation) can result in consequences ranging from soft tissue impacts to death. However, such outcomes are rare and typically occur in occupational settings (see the section ‘Occupational exposure’). In terms of general environmental exposure, the main concerns are endemic dental and skeletal fluorosis that affect significant populations around the world.

Dental Fluorosis

Following the connection between mottled enamel and excess fluoride in drinking water established by Smith and co-workers in the 1930s, dental fluorosis was recognized as an irregular calcification disorder (hypomineralization) of the enamel

and dentin due to the incorporation of excessive fluoride in these structures. Fluorosed enamel is porous, often stained and has brown pits and in its more severe form, is brittle and prone to erosion and breakage (Figure 1). Subsequently, dental fluorosis has been reported from many regions, commonly associated with drinking water contents > 1.5 mg L^{-1} fluoride. It should be noted, however, that conditions vary and water is not always the main exposure route.

The severity of the condition is thought to reflect the extent of fluoride exposure during enamel formation in the pre-eruptive phase of tooth development (usually birth – 8 years) and can affect both temporary and permanent teeth. At the end of tooth development and mineralization, the enamel and dentin become less penetrable for fluoride ions; therefore the rate of inclusion and mobilization of fluoride slows dramatically. Fluoride is incorporated into dental tissues via blood-cell formation through pulp and saliva (or water) contact with the upper enamel layers. However, the staining and pitting of dental enamel are thought to occur post-eruption as a result of enamel matrix disruption.

The mechanism of change in dental hard tissue due to fluoride excess is still open to debate. Sodium fluoride (NaF) is known to inhibit protein synthesis, which has lead most workers to believe that fluoride cell toxicity is due to this mechanism. Fluoride is thought to affect the enamel secretion cells while the outer layer of the tooth is under development, disrupting the formation of normal enamel. Collagen is the most widespread protein in the human body and fluoride induces the formation of active oxygen metabolites, which disturb collagen biogenesis. Since collagen is one of the most important foundations of bone formation, interruption of the collagen metabolism could affect dental development.

Other workers have suggested that dental fluorosis occurs as a result of fluoride interaction with calcium, magnesium, manganese and other elements in the dental hard tissues, which destroys the biologic activity of the these elements leading to enamel injuries. Some studies have shown a possible reduction in calcium content during tooth mineralization, leading to the destruction of dental tissue structure. However, there is conflicting evidence as to whether changes in calcium and phosphorous enamel contents occur as a result of excess fluoride exposure.

It has also been suggested that dental fluorosis is related to the more aggressive chemical activity of fluoride compared to iodine such that fluoride reduces the amount of iodine in the thyroid gland resulting in functional disorders. Studies demonstrate that ingested fluoride is absorbed quickly into the blood and blocks thyroid activity. It should be noted, however, that even if fluoride is both chemically and biologically iodine-antagonistic, it does not influence goiter prevalence.

Depending on the severity of fluorosis, dental injuries can manifest as chalk-like lines (line form) and spots (spot form) in various places over the tooth-crown; spot pigmentation from light yellow to dark brown; small defects in the enamel on the background of spots (chalk-like-dot form); more pronounced defects (erosive form) and the complete destruction of dental enamel and wearing down of teeth (destructive form). Increased fragility of hard dental tissues during fluorosis leads to the brittle fracture of crowns. Various schemes to assess the severity of dental fluorosis have

been devised, the most common of which is Dean's Index (Table 1). Milder forms of the disease are often barley detectable and are considered a cosmetic effect.

Many studies demonstrate that the severity of dental fluorosis depends primarily on the following factors:

1. Fluoride uptake (particularly in water)
2. Duration of exposure
3. Child nutritional characteristics age 1-2 years
4. Physiological status
5. Sensitivity to fluoride intoxication

Endemic fluorosis regions are often characterized by a reduction in the prevalence and intensity of dental caries. However, during intake of very high concentrations of fluoride, the anti-caries effect is lost due to the prevalence of severe fluorosis causing increased fragility and breaking of enamel. Under these conditions, the dentin becomes exposed and destructive processes, which closely resemble dental caries, are observed.

Skeletal Fluorosis in Adults

Fluoride also affects the human skeletal structure. Endemic skeletal fluorosis is a chronic metabolic bone and joint disease caused by intake of large amounts of fluoride either through water or less commonly from foods/air in endemic areas. Although not the only exposure route, skeletal fluorosis has most often been reported in populations consuming > 3-5 mg L^{-1} in drinking water.

As in the case of teeth, human bones are composed of hydroxylapatite but this mineral and fluorapatite are end-members in the apatite solid solution series. Therefore fluoride exchanges readily with the OH^- ion in the apatite structure increasing the brittleness and decreasing the solubility of the bone mass. Within the bone structure, fluoride accumulates most effectively in growing cells due to better hydration of the tissues and richer blood supply. Small apatite crystals on the bone surface also enable rapid inter-crystal and surface fluoride metabolism. Within the same skeleton, fluoride contents in different types of bone vary. Most fluoride is found in bones containing abundant spongy tissue.

Fluoride has a strong attraction for calcium ions in the body and binds calcium in the bone structure. Hence, calcium excretion from other tissues is increased resulting in an almost constant negative calcium balance. Fluoride ions increase bone-forming cell activity and enhance accretion, resorbtion and bone turn-over. Since the bones of the human body are constantly resorbed and redeposited during a life-time, high fluoride intakes disrupt the stability of bone mineral metabolism leading to osteosclerosis (bone hardening). Several studies have shown that skeletal fluorosis patients retain far more calcium in bone than control groups. The result is a range of skeletal deformities including fixed spine, kyphosis (curvature of the spine) and genu valgum (knock knees). Calcification of soft tissues such as ligaments can also occur (Table 2).

There is a direct correlation between age and bone fluoride content. Although ingestion of fluoride may occur over a lifetime, after a number of years bones become saturated with fluoride (although the human organism can never create pure fluorapatite) and a dynamic equilibrium is established. Some studies suggest a fluoride plateau appears after 50-55 years but there are other data that show fluoride contents in bones in older people continue to increase very slowly. If the fluoride intake drops, then the concentration in blood is reduced and the body remobilizes fluoride deposited in bones. Over this time, which lasts about two years, fluoride secretion reduces exponentially. Reduced metabolic rates in later life are also thought to increase the resorbtion time of fluoride from bones.

Although approximately 80 % of fluoride entering the body is excreted mainly in the urine, the remainder is absorbed into body tissues from where it is released very slowly. Therefore, repeated or continuous exposure to fluoride causes accumulation in the body. Fluoride is a cumulative toxin and unlike dental fluorosis, skeletal fluorosis is considered to be an indicator of long-term exposure commonly affecting older members of the population. However, crippling forms of the disease are also seen children in endemic areas. Hyperthyroidism is a secondary effect of the condition.

Numerous studies have demonstrated links between high fluoride intake from water and other sources and bone fluoride composition. However, fluoride contents also depend upon personal characteristics such as age and health, living conditions, length of exposure, nutritional status and exposure to ultra-violet light (Vitamin D generation). Low calcium intake has been shown to exacerbate the effects of fluoride on bone turnover and can result in rickets and osteomalacia (bone softening).

Skeletal Fluorosis in Children

The pharmacokinetics of fluoride in children are characterized by a positive balance. Under normal conditions, fluoride mobilization from blood plasma to bone tissue is greater than between plasma and excretion in the urine. The amount of fluoride resorbed into plasma from the bone tissue in children is greater than that in adults. Although, the fluoride balance is normally positive in children, factors such as age, fluoride content in dinking water, food and air, etc. can result in either positive or negative balances.

Bone mass accumulation in children is very dependant on age, genetic factors and gender. As a consequence of the rapid rate of growth and bone tissue metabolism, children dwelling in territories with increased fluoride contents in drinking water/foods/air very often exhibit inhibited physical maturity. This is due to exposure at sensitive bone developmental stages particularly the pre- and postnatal period, the first year of life and during puberty. Several studies comparing children with identical social and domestic conditions in endemic fluorosis regions and control groups demonstrate the greater prevalence of children of below average height in fluorosis areas.

Indeed, changes in the skeletal structure can be induced by relatively small doses of fluoride. Therefore, children are more susceptible to fluoride intoxication than adults. Childhood clinical symptoms include rickets, osteoporosis and disorders of the calcium steady-state balance. Studies have shown that in children with calcium

deficient diets, bone tissue disorders were observed in 90 % of subjects whereas in children receiving > 800 mgCa day^{-1} only 25 % developed symptoms of fluoride intoxication. In areas of calcium deficiency, evidence of skeletal fluorosis has been found in children drinking water with less than 2.5 mg L^{-1} fluoride.

Skeletal Fractures

The connection between high fluoride intakes and skeletal fractures has been investigated in many studies. However, the data are equivocal with several studies reporting beneficial effects of fluoride against fracture rates and other studies reporting increased fracture rates in high-fluoride populations. Studies examining total fluoride exposure, but particularly fluoride in drinking water, versus all fracture rates in China demonstrated a U-shaped dose-response curve. Higher fracture rates were associated with drinking water intakes below 0.34 mg L^{-1} and above 4.32 mg L^{-1} fluoride, the latter in populations exposed to 14 mgF day^{-1}.

Cancer

Large numbers of studies have been carried out in numerous countries to assess relationships between high-fluoride environmental exposure and cancer. However, there is no clear evidence of increased cancer morbidity or mortality associated with exposure via water/food/air. Increased mortality and prevalence of lung, liver, bladder, stomach, esophagus, pancreas, lymphatic, prostate and brain cancers have been reported in occupationally exposed workers in the aluminum and cryolite industries. However, the results are inconsistent and these health effects are most likely to result from concurrent exposure to other substances. To date, studies in laboratory animals have not demonstrated that fluoride is carcinogenic.

Other Health Effects

At very high doses usually associated with acute exposure, fluoride interferes with carbohydrate, lipid, protein, vitamin, enzyme and mineral metabolisms and can lead to hemorrhagic gastroenteritis, acute toxic nephritis and damage to the liver and kidneys. Respiratory irritation, pulmonary edema, cardiac arrests and death have also been reported. Owing to the inhibition of cholinesterase glycolysis (breakdown of carbohydrates) and the formation of complex fluoride and calcium compounds in extracellular fluids; such metabolic disorders are observed as hyperkalemia (high blood potassium), hypocalcemia (low blood calcium) and hypomagnesemia (low blood magnesium). Fluorine and hydrogen fluoride are highly reactive chemicals and direct contact with the body can also result in severe skin and eye damage.

The effects of general environmental fluoride exposure on human soft tissue homeostasis are equivocal. Long-term occupational exposure to fluoride has been reported to reduce the iodine accumulation activity of the thyroid resulting in a reduction in triiodothyronine production, an increase in thyrotropic hormone levels in blood-serum and irregularities of the androgen status (subclinical hypothyrosis). There is some evidence that continuous fluoride intoxication provokes hypertension and chronic ischemic heart disease. Some studies have shown that clinically acute fluoride intoxication manifests as nausea, sickness, diarrhea, stomach ache and heart rate disorders at concentrations of 6.5-20 mgF L^{-1} in water. However, there is no

conclusive evidence that general fluoride exposure results in respiratory, hepatic, renal, reproductive or genotoxic effects.

Etiology of Fluoride Health Issues

Humans may be exposed to fluoride in air via inhalation, through dermal contact and via the ingestion of soil, food, dental products and water. Fluoride is also utilized in a number of industrial processes that release the element to the environment and can result in occupational exposure.

The level of toxicity depends on the exposure route and form of fluoride. Fluorine (F_2) and anhydrous hydrogen fluoride (HF) are naturally occurring gases whereas the aqueous form, hydrofluoric acid (HF_{aq}) is one of the most corrosive substances known to man. Sodium fluoride (NaF) and calcium fluoride (CaF_2) are the most common mineral salts. Sodium fluoride is more soluble than calcium fluoride and is used in dental products and water fluoridation as well as fluorosilic acid and sodium hexafluorosilicate (Table 3). The fluoride ion (F^-) is the toxicologically active agent hence reactive compounds such as oxygen difluoride (OF_2) are highly toxic whereas salts such as sodium and calcium fluoride are less so. In general, the more soluble the fluoride compound, the more toxic it is as it can be readily absorbed via oral ingestion. The primary exposure routes for fluorine gas and hydrofluoric acid are acute occupational dermal contact and inhalation whereas for most fluoride compounds the main concern is chronic oral exposure in drinking water, food and dental products.

Acute Exposure

In terms of oral ingestion, some acute intoxication incidents have occurred in fluoridated water supplies as a result of accidental overdosing resulting in fluoride concentrations of 30-1000 mg L^{-1}. It is estimated that to produce acute symptoms such as nausea, vomiting and gastric pain, requires oral intakes of at least 1 mg kg-bodyweight^{-1} of sodium fluoride and that 32-64 mg kg-bodyweight^{-1} is the lethal dose (Table 4). Via inhalation, acute exposures to relatively low concentrations of hydrogen fluoride ($\geq$ 0.5 ppm) or fluorine gas ($\geq$10 ppm) result in respiratory tract and ocular effects in humans. Although no dose-response relationships have been established for dermal exposure, skin lesions have been reported following contact for a minimum of an hour with 2 % hydrofluoric acid.

Occupational Exposure

Industrial sources of fluoride compounds include coal combustion; steel, glass, brick, ceramic and glue manufacture; aluminum, copper, nickel and phosphate processing and fertilizer and pesticide production and use (Table 3). Occupational exposure to fluoride via inhalation or dermal contact is most likely to occur in welding operations and aluminum, steel and phosphate production. Indoor air concentrations $\leq$ 16 500 µg m^{-3} have been reported in these settings which exceed the recommended exposure levels for fluoride (Table 4). Occupational dermal exposure to hydrofluoric acid has been reported to result in severe tissue damage, respiratory effects, cardiac arrests and death. Cardiac effects and death are thought to result from hypocalcemia and hyperkalemia. Eye, throat, chest irritation and vomiting have also been observed in

workers exposed to sulfur hexafluoride. Although increased incidence of cancer, skeletal and respiratory effects have been reported in industrial settings, the workers were exposed to a variety of other substances and conclusive evidence for the role of fluoride in these health effects has yet to be established.

Dental-Product Exposure

Fluoridated dental products generally contain 1000-1500 mg kg^{-1} fluoride and have been identified as significant sources of fluoride intake, particularly in children. Studies estimate intakes of 50 µg per brushing and 2 mg per use with mouthwash. Swallowing toothpaste is thought to contribute 0.50-0.75 mg day^{-1} fluoride in children. As a result, low-fluoride products (250-500 mg kg^{-1}) have been developed for children and are available now in many countries.

Environmental Exposure

Air

Fluorides are widely distributed in air in both particulate and gaseous form. The degree of toxicity of different chemical species is in the order $F_2 > OF_2 > HF > H_2SiF_6 > BF_3$ whereby gaseous fluorides are more toxic than particulates in air. Fluorides are derived from natural sources such as marine aerosols, volcanic emissions and continental dusts as well as industry including the production of phosphate fertilizers, coal ash and burning fuels. However, in non-industrial areas, concentrations in ambient outdoor air are typically 0.05-1.90 µg m^{-3} with average exposures of < 1 µg m^{-3}, which are insignificant in normal circumstances. In areas where high-fluoride coal products are burned or phosphatic fertilizers are produced, exposure via inhalation can cause health problems. Human fluorosis has been reported in parts of China due to the burning of fluoride-rich coal products resulting in household air contents ≤ 155 µg m^{-3} (see the section 'Foodstuffs, diet and drinking water').

Rocks, Soils and Waters

In the natural environment, fluorides are released through the weathering and dissolution of rock and soil minerals; from volcanic emissions and in marine aerosols.

The distribution of fluoride in the natural environment is not uniform but is influenced by geogenic processes and presence of fluoride-bearing minerals. Fluorides are found in a number of common rock-forming minerals including fluorspar or fluorite (CaF_2); rock phosphates (e.g. fluorapatite: $Ca_5(PO_4)_3F$); cryolite (Na_3AlF_6); micas and hornblende. Typical concentrations in soil range from 20-1000 mg kg^{-1} although these can be higher in mineralized areas or due to fertilizer use and volcanic or industrial emissions. In solution, the element forms F^- ions and concentrations in water are often limited by the solubility of the mineral fluorite (CaF_2). Therefore high-fluoride waters are commonly associated with calcium-poor conditions and where substitution of calcium by sodium occurs. High pH thermal waters also tend to be rich in the element. Concentrations in surface water (< 0.5 mg L^{-1}) and seawater (1.2-1.5 mg L^{-1}) tend to be lower than those in groundwater (1-10 mg L^{-1}) due to longer residence times for rock-water interactions. However, concentrations in water are highly variable depending on local conditions and values of 2800 mg L^{-1} in sodic lakes and

50 mg L^{-1} in groundwater have been reported in volcanic regions of East Africa. Indeed high-fluoride environments are typically associated with volcanic rocks, marine sediments and granite and gneissic rock types and occur in many areas of the globe including the Mediterranean; southern Europe and Russia, the Middle East, the East African Rift from Jordan to Tanzania, West and southern Africa, India, Pakistan, Thailand, China and the southern USA. Human dental and skeletal fluorosis affect millions of people in many of these areas as a result of exposure to high-fluoride drinking waters (See WHO (2006); Edmunds and Smedley (2005)).

Foodstuffs, Diet and Drinking Water

Fluoride in soil is generally poorly soluble, hence uptake into crops depends not only on the concentrations in the soil (uptake via the roots) but on the levels of atmospheric deposition of the element (uptake via the stomata directly into the plant leaf structure). Indeed, fluoride is found in higher concentrations in the leaves of plants relative to other components. Although fluoride is found in fluoroacids and nucleocidine it is not essential to bacteria, algae, fungi and higher plants. Therefore, many crops accumulate very little of the element and vegetables and fruits normally contain low concentrations (< 0.4 mg kg^{-1}). However, different plant species uptake the element to varying degrees and some cereals such as barley, rice, taro, yams and cassava can contain higher concentrations (~ 2 mg kg^{-1}). Tea is also relatively enriched in the element and can contain 400 mg kg^{-1}. Tea is recognized as a significant exposure route with typical intakes of 0.04-2.70 mg $person^{-1}$ day^{-1}. Indeed dental fluorosis has been reported in Tibetan populations due to the consumption of brick tea that is made from older leaves with higher fluoride contents resulting in intakes of 14 mg day^{-1}. Some fruit juices contain elevated concentrations as fluoride is used as a pesticide during crop growth. Similarly wines can also contain relatively high quantities of the element (≤ 6.34 mg L^{-1}).

Dental and skeletal fluoroses have also been reported in populations consuming crops such as maize and chilies that are dried over fluoride-bearing coal products in southern China. In order to conserve resources, pulverized coals are mixed with locally sourced clays to produce fuel briquettes. The coals contain relatively high amounts of fluoride (100-300 mg kg^{-1} compared to 50-100 mg kg^{-1} in most coals). However, several more recent studies have shown it is the clays that are highly enriched in the element (> 1000 mg kg^{-1}). Not only the burning of the resultant briquettes leads to very high indoor air exposure (see the section 'Air'), but the drying of foodstuffs also increases the fluoride content of crops enormously (Table 5). As a result of this combined inhalation and ingestion exposure, it is estimated that dental fluorosis affects 10 million and skeletal fluorosis 1.5 million people in this region. Now that the role of clays in fluoride exposure is understood, this will aid the development of future mitigation strategies.

Fluoride primarily accumulates in the skeletal tissues of grazing animals, therefore, levels in meat are generally low (< 1 mg kg^{-1}). Seafood contains marginally higher amounts with concentrations in fish ranging from 2-5 mg kg^{-1}. Despite the fact that fish protein may contain up to 370 mg kg^{-1} fluoride and fluoride accumulates in the bones of canned fish, which are also eaten; even in mixed diets with relatively high fish consumption, it is estimated that the average daily fluoride intakes are only about 0.2 mg.

The fluoride content of cows' milk (0.02-0.06 mg L^{-1}) and human breast milk (0.005-0.010 mg L^{-1}) is also generally low; hence these do not contribute significantly to dietary intake. Evidence suggests that concentrations in infant formulae are higher (0.1-1.6 mg L^{-1}) and studies carried out in six countries demonstrated that formula made with distilled water supplied 30 µg day^{-1} fluoride to 3 month old babies. Some studies have reported dental mottling in infants receiving 0.5 mg day^{-1} fluoride from baby formulas.

Other exposure routes include the use of fluoride-contaminated trona ($Na_3H(CO_3)_2.2H_2O$) known as magadi salt in the cooking process in Tanzania resulting in dental fluorosis in the local populations. Comparisons between two endemic regions with water supplies containing 0.2-0.8 mg L^{-1} fluoride showed lower dental fluorosis rates (7-46 %, no severe forms) in coastal communities despite the fact that they consumed more fish and tea than in inland villages where the magadi was used (53-100 %, severe forms highly prevalent 18-97 %).

With the exception of tea, magadi salt and the dried foodstuffs in China, exposure to fluoride in foodstuffs is generally considered less important than water as the fluoride content of most foods is low (< 10 mg kg^{-1}). Furthermore, more than 90 % of the fluoride present in water is absorbed in the human body compared to only 30-60 % in foodstuffs. Even fluoride in liquid products (milk, etc.) is assimilated 10 % less than in water.

Therefore, the WHO determines that in most situations, drinking water is a major pathway for fluoride to enter the human body. In response to the potentially harmful effects of the element, the WHO has set a drinking water quality maximum admissible concentration (MAC) of 1.5 mg L^{-1} (Table 4). Numerous clinical and experimental studies show a variety of influences of fluoride on human health depending upon the content in drinking water. Research has shown that fluoride concentrations between 0-0.5 mg L^{-1} are associated with increased rates of dental caries whereas contents between 0.5-1.5 mg L^{-1} have a beneficial effect, reducing caries. Concentrations between 1.5-5 mg L^{-1} can result in dental fluorosis. Ingestion of 5-40 mg day^{-1} fluoride via drinking water can produce skeletal deformities and knock knees (genu valgum) have been reported in adolescents receiving > 10 mgF day^{-1} in water from birth.

It is estimated that more than 260 million people globally consume drinking water containing > 1.5 mg L^{-1} fluoride many of which live in tropical countries. As outlined in the section 'Rocks, soils and waters'; endemic dental and/or skeletal fluorosis are associated with many of these regions and approximately 25 million people suffer from fluorosis in India alone. In poorer parts of the world prevalence rates of these diseases may be upward of 90 % in affected villages. Populations suffering dental fluorosis are sometimes culturally ostracized limiting the ability to marry and have family security. Skeletal fluorosis seriously inhibits the ability of populations to work, contribute to the economy, produce their own food and support their families to the major detriment of poor communities. Hence both these diseases have serious impacts in developing countries in particular. As a result of these concerns, numerous methods to remove fluoride from drinking water have been implemented with varying degrees of success depending on their sustainability and appropriateness of technology to recipient populations. Excellent summaries of these methods exist in the literature.

However, in several cases alternative low-fluoride waters may be available should the resources exist to identify and exploit them.

Human exposure from fluoride in drinking water depends not only on the concentration but on the levels of daily water intake. The WHO guidelines are based on a daily consumption of 2 L, however, intake varies significantly between temperate and tropical climates and between individuals depending on levels of exercise, health and preference. For example, numerous studies have demonstrated the occurrence of dental fluorosis in populations exposed to < 1.5 mg L^{-1} in drinking water, and not all populations exposed to 3 - 5 mg L^{-1} in water develop skeletal fluorosis. Hence these limits are a guide only to be modified in different circumstances. Typical estimates of total adult intake in non-fluoridated water areas in temperate regions are of the order 0.6 mg day^{-1} although this can rise to 2 mg day^{-1} in fluoridated zones.

Many studies demonstrate that the prevalence and severity of fluorosis are influenced by complex interactions between dietary factors and the pH of the stomach contents. Total fluoride absorption in the human body not only depends upon the concentration in water but on the proportion of liquid to solid matter (food) consumed and the composition of the food. In the stomach under acid conditions, up to 40 % of the ingested fluoride can be absorbed following conversion to hydrogen fluoride (HF). Fluoride that is not absorbed in the stomach is subsequently ingested in the upper intestine independent of pH. Dental fluorosis is thought to develop when > 0.10-0.15 mgF kg-$bodyweight^{-1}$ is absorbed.

Studies have shown that soluble compounds, such as sodium fluoride (NaF), hydrogen fluoride (HF), fluorosilicic acid (H_2SiF_6) and sodium monofluorophosphate (Na_2FPO_3), release fluoride easily, which is almost completely absorbed. However, the intake of cations such as calcium, magnesium and aluminum - which form relatively insoluble compounds with fluoride - has a protective effect against absorption. In contrast, the presence of phosphate and iron may enhance absorption. Protein deficiency is thought to enhance the effects of fluorosis as proteins aid the absorption of calcium in the body. Studies in China and Moldova of communities with similar fluoride intake but differing nutritional status, demonstrated that populations with lower calcium and protein diets suffered more fluorosis. In addition to the influence of proteins, there is some evidence to suggest that high fat diets may exacerbate the adverse health affects of fluoride. Vitamins C and D have also been implicated in the pathogenesis of fluorosis. Vitamin C aids the hydroxylation of proline, one of the most important amino acids of the basic bone building material collagen. Hence, healthy collagen is required if bones are to be calcified correctly. Vitamin D is known to aid calcium absorption in the body and deficiency has been both suggested and disputed as a contributory factor in fluorosis in India. These complex dietary interactions may in part explain why fluorosis is prevalent in some populations but not in others consuming similar levels of fluoride.

In summary, although the biologic mechanisms are not yet fully understood, the links between high environmental fluoride and human dental and skeletal fluorosis and low environmental fluoride and dental caries have been well established. The severity of clinical response to high fluoride intakes is determined by a variety of factors such as general nutritional status, length and timing of exposure and genetic status. In all these diseases, one of the most important exposure routes is drinking water. No

effective cures are available for dental or skeletal fluorosis, however, the diseases are preventable if fluoride intake is controlled. Hence the need for better understanding of the complex interactions between dietary, drinking water and inhalation exposure for caries prevention on the one hand and debilitating fluorosis on the other.

Further Reading

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Web-based Resources

World Health Organization, Geneva, Switzerland. Web: http://www.who.int/en/

International Society for Fluoride Research. Web: http://www.fluorideresearch.org/

Centre for Disease Control (USA) Recommendations For Using Fluoride. Web: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm

Agency for Toxic Substances and Disease Registry (USA) Toxicology Profiles. Web: http://www.atsdr.cdc.gov/toxprofiles/

Table 1. Dean's index to assess the severity of dental fluorosis

Classification	Criteria – Description of Enamel
Normal	Smooth, glossy, pale creamy-white translucent surface
Questionable	A few white flecks or white spots
Very Mild	Small opaque, paper white areas covering less than 25% of the tooth surface
Mild	Opaque white areas covering less than 50% of the tooth surface
Moderate	All tooth surfaces affected; marked wear on biting surfaces; brown stain may be present
Severe	All tooth surfaces affected; discrete or confluent pitting; brown stain present

From: Dean (1942)

Table 2. Clinical Phases of Skeletal Fluorosis

Osteosclerotic Phase	Bone Ash F Concentration mg kg^{-1}	Symptoms
Normal Bone	500 to 1000	Normal
Preclinical Phase	3500 to 5500	Asymptomatic; slight radiographically-detectable increases in bone mass
Clinical Phase I	6000 to 7000	Sporadic pain; stiffness of joints; osteosclerosis of pelvis and vertebral spine
Clinical Phase II	7500 to 9000	Chronic joint pain; arthritic symptoms; slight calcification of ligaments; increased osteosclerosis and spongy bones; with/without osteoporosis of long bones
Clinical Phase III: Crippling Fluorosis	> 10 000	Limitation of joint movement; calcification of ligaments of neck vertebral column; crippling deformities of the spine and major joints; muscle wasting; neurological defects/compression of spinal cord

Compiled from: US-PHS (1991) and ATSDR (2003)

Table 3. Common inorganic fluoride compounds and their industrial uses

Fluoride Compound	**Industrial Use**
Anhydrous Hydrogen Fluoride (HF) Fluorine (F_2) gas	Production of synthetic cryolite (Na_3AlF_6), aluminum fluoride(AlF_3), gasoline alkylates and chlorofluorocarbons
Hydrofluoric Acid (HF_{aq})	Etching semi-conductors and glass Cleaning brick, glass and aluminum Tanning leather Rust removal
Calcium Fluoride (CaF_2)	Flux in steel, glass, aluminum and enamel production Production of hydrofluoric acid (HF_{aq}) and anhydrous HF
Sodium Fluoride (NaF)	Flux in steel, glass, aluminum and enamel production Preservative in glue and wood Pesticide
Sulfur Hexafluoride (SF_6)	Electronic components Magnesium and aluminum production
Sodium Hexaflourosilicate (Na_2SiF_6)	Fluoridation of drinking water
Fluorosilicic Acid (H_2SiF_6)	Fluoridation of drinking water
Fluorapatite $Ca_5(PO_4)_3F$	Phosphates and fertilizer
Sodium Monofluorophosphate (Na_2FPO_3)	Dental products
Stannous Fluoride (SnF_2)	Dental products

Compiled from: ATSDR (2003) and WHO (2002)

Table 4. Human exposure indicators for fluoride in various media

Substance	Exposure	Guideline	Reference
Sodium Fluoride	Total Intake	32-64 mg kg-bodyweight^{-1}	Lethal Dose
Fluorine	Air	200 µg m^{-3} (TWA)	US NIOSH REL
Hydrogen Fluoride	Air	2500 µg m^{-3} (TWA)	US NIOSH REL
Sodium Fluoride	Air	2500 µg m^{-3} (TWA)	US NIOSH REL
Fluorine	Air	20 µg m^{-3}	Acute Inhalation US MRL
Hydrogen Fluoride	Air	20 µg m^{-3}	Acute Inhalation US MRL
Fluoride	Oral Intake	10 – 20 mg day^{-1}	Skeletal fluorosis
Fluoride	Oral Intake	0.05 mg kg^{-1} day^{-1}	US MRL
Fluoride	Water	5-10 mg L^{-1} for 10 years	Skeletal fluorosis
Fluoride	Water	0.5 mg L^{-1}	Water guideline minimum to prevent dental caries[a]
Fluoride	Water	0.5 – 1.5 mg L^{-1}	Water guideline optimum, no adverse health effects and dental caries decreases[a]
Fluoride	Water	1.5 mg L^{-1}	Water guideline MAC to prevent dental fluorosis[a]
Fluoride	Water	3 mg L^{-1}	Water guideline level above which skeletal fluorosis may occur[a]

TWA = Time Weighted Average
US MRL = United States Minimal Risk Level
US NIOSH REL = United States National Institute for Occupational Safety and Health Recommended Exposure Level
MAC = Maximum Admissible Concentration
a = World Health Organization Drinking Water Guidelines based on consumption of 2 L per day

Table 5. Effect of drying food over high-fluoride briquette fires in southern China

	Coal	Clay	Briquette	Fresh Chilies	Dried Chilies	Fresh Maize	Dried Maize
F mg kg^{-1}	237	2262	828	0.79	110	1.64	1419

Compiled from: Dai et al. (2007)

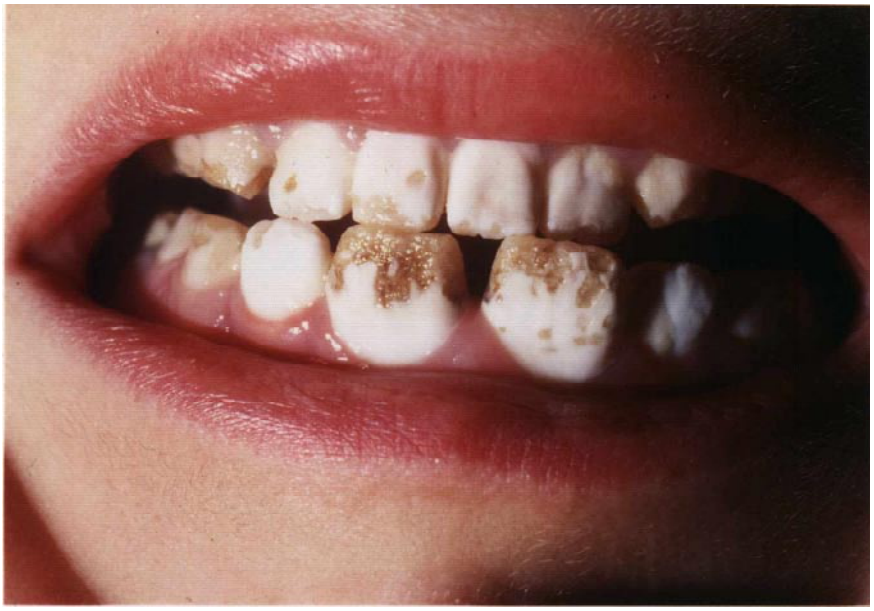

Photo: Prof V Povoroznuk, from: Fordyce et al. (2007)

Figure 1. Severe dental fluorosis caused by intake of drinking water with ≤ 2.43 mgF L^{-1}.