FLUORIDE TOXICITY – A HARSH REALITY
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**ABSTRACT**
There are many incidents of fluoride toxicity whether it is acute or chronic. Fluoride toxicity is an environmental hazard which arises from the upper layers of geological crust and is dissolved in water. Prolonged drinking of such water causes chronic fluoride toxicity. Use of fluoride containing compounds for various purposes such as dental products, metal, glass, refrigerator and chemical industries act as a source of fluoride poisoning and increase the risk of toxicity. This review reflects the deleterious effects of fluorides on various organs in the physiological system.

**KEYWORDS:** Fluorosis, fluoride toxicity, skeletal effects, soft tissue effects, neurobehavioral effects.

**INTRODUCTION**
The proportion of water in the human body ranges from 50% to 75% (55% in females, 60% in males and 75% in children approximately), making water a vital constituent needed by the body to maintain homeostasis. The composition of ground water can vary as it is often controlled by an interaction between soil and the rocks and drinking such water will have a great impact on human health. Both deficiency and excess of minerals and trace elements in water can have deleterious consequences on biological systems. Consumption of fluoride containing water for 10 to 12 years can enhance the risk of developing “fluorosis”. Children are most vulnerable to discoloration of teeth from chalky white to yellow or brown with pitting referred to as ‘dental fluorosis’ and people above 45 years are more susceptible to swollen joints, deformed and enlarged bones referred to as ‘skeletal fluorosis’. Fluorosis occurs rapidly after the onset of high fluoride water ingestion and children are the mostly affected vulnerable to its deleterious effects.

Fluoride in groundwater is mainly derived from the weathering of rocks. In geothermal waters and volcanic zones, fluoride concentrations are related to the development of hyper alkaline volcanic rocks, the melts and volatile fractions of which accumulate large contents of fluoride. In crystalline bedrock aquifers, fluorine occurs in primary minerals and is ubiquitous, especially in biotite and amphibole as a substitution for hydroxyl positions; it may also occur within mineralized veins. In sedimentary basins, the sources of fluoride are mainly fluorite (CaF$_2$), fluoroapatite (Ca$_5$ (PO$_4$)$_3$F), and marine clays on which fluoride may be adsorbed. Other sources of fluoride in groundwater are anthropogenic inputs which increase fluoride concentrations in rain, including chlorofluorocarbons (CFCs) and other industrial emissions – especially those produced from coal burning, brick making and aluminium smelting. Concentrations in rainfall are low (<0.2 mg/l) compared to concentrations in groundwater, but evapotranspiration leads to an increase in fluoride concentration before reaching the water table.

Fluorine is a halogen which is the most electronegative and one of the most reactive of all the elements. Generally, it does not exist in the elemental state in nature and in combination it comprises 0.065% of the earth’s uppermost crust. Fluorine forms numerous inorganic salts and also occurs in countless organic compounds, substituting for hydrogen. Fluorides are used in wire and cable insulations, pipe linings, as rocket propellants, rodenticides, refrigerants, aerosol propellants, polymers for plastics, in the separation of uranium isotopes, and in the aluminum, beryllium, antimony, superphosphate fertilizer, glass, electronic ceramics, fluorospar, and the brick industries.

Fluorides in the atmosphere arise from fluoride containing dusts, volcanic gases and wastes from the industry and burning of coal fires. In nonindustrial urban areas, the highest fluoride quantity available for inhalation is approximately 0.04 mg/day but near fluoride emitting factories this could increase to 4 mg/day. Fluoridated toothpastes can provide another
major source of fluoride intake, particularly to children. Toothpastes contain 1.0 to 1.5 mg fluoride per gram and based on estimates of an average ingestion of 0.5 g toothpaste per use for 2 to 5 year old children could result in the intake of 0.50 to 0.75 mg fluoride per use. For 7 to 13 year olds the estimate was 0.4 to 1.2 mg fluoride per use. Fluoride containing mouth wash could contribute 0.2 to 0.4 mg fluoride per use. Fluoride tablets and topical gels represent additional sources of fluoride exposures. Different forms of fluoride were shown in Figure 1.

HISTORICAL PERSPECTIVE

During the latter half of the 19th century and the first half of the 20th century, sodium fluoride was commonly used as a pesticide in US homes and institutions. It was often stored in the kitchen or other places where the residents had access to the compound. Because of this, many cases of accidental or intentional acute fluoride poisoning were occurred. There are several mass poisonings occurred at the Oregon State Hospital. One of them is when an evening meal of scrambled eggs was prepared with sodium fluoride which had been mistaken for powdered milk. Approximately 17 pounds of sodium fluoride were added to 10 gallons of eggs. There were 263 cases of acute poisoning, of which 47 terminated fatally. Other similar incidents in which sodium fluoride was mistaken for sodium bicarbonate or corn starch have been recorded. In 1965, Hodge and Smith noted that there were more than 600 fluoride induced deaths in the US since 1933, and that approximately 1% of all fatal poisonings were due to fluoride. Currently, fluoride compounds are almost obsolete for domestic use; however, dental products containing fluoride compounds are still in use. This is one of the reasons for decrease in the incidence of acute fluoride poisoning.

Chronic toxicity

The only known adverse effect associated with the ingestion of relatively low levels of fluoride (1-2 ppm in the drinking water) on a chronic basis is dental fluorosis. Signs of skeletal fluorosis become evident on consumption of 8-10 ppm of fluoride in drinking water for approximately 10 years or more.

PHARMACOKINETICS

Fluoride is predominantly absorbed through the gastrointestinal and respiratory tracts however dermal absorption is negligible except in cases of hydrofluoric acid burns. Fluoride readily crosses the placenta and is absorbed by the fetus. At birth, infant serum fluoride levels are approximately 75% of maternal levels. Soluble fluoride compounds are rapidly and almost completely absorbed to an extent of 90 to 95% across the gastrointestinal tract with peak serum levels achieved after 30 min of ingestion on a fasting stomach. The rate of absorption could be altered when fluoride is ingested with food or complexed with certain inorganic salts (e.g., calcium, phosphate, magnesium, aluminum). If conditions are favorable, 90% of ingested fluoride is absorbed in the stomach. Metallic ions like calcium, iron and magnesium in the diet complex with fluoride ion and can retard the fluoride absorption.

The large volume of extracellular body fluids dilutes the absorbed fluoride concentration; there by avoiding elevation in plasma fluoride concentration. From the plasma, fluoride diffuses to the tissues throughout the body. Approximately 50% of the daily fluoride intake is deposited in calcified tissue which encompasses teeth and bone. Skeletal fluoride accounts for approximately 99% of the body burden, with the remainder distributed between blood and soft tissues. The half-life of fluoride in plasma ranges from 2 to 9 h, depending on the dose level and can accumulate for several years in bone. Mean plasma ionic fluoride concentrations among persons living in communities with non fluoridated drinking water supplies (<0.3 mg/l in drinking water) range from 0.004 to 0.02 mg/l. In optimally fluoridated communities (0.7 to 1.2 mg/l), they range from about 0.02 to 0.04 mg/l. The highest tissue concentrations occur in the skeleton and in the kidney, reflecting the body’s major pathways of removing fluoride. Both processes proceed quickly, but skeletal deposition is the more rapid of the two in young individuals. Amount of fluoride removed by each process varies greatly depending on the state of skeletal maturation. In adults of minimal skeletal growth, only about 10% of ingested fluoride is deposited in the bone, whereas in growing children more than 50% may be incorporated in bone. Fluoride is excreted largely by the kidneys with 40 to 60% of the daily fluoride dose excreted in urine showing an elimination half-life of about 5 h. Fluoride is also eliminated in sweat, breast milk, and saliva.

EFFECTS ON GASTRIC MUCOSA

The stomach is a target organ for the adverse effects of fluoride. Among the soft tissues of the body, the propensity of gastric mucosa exposed to the highest concentrations of the ion is immense. The threshold fluoride concentration for disruption of canine gastric mucosal barrier function is between 1 and 5 mol/l or 19 and 95 ppm. Nausea and vomiting have been reported in dental patients particularly children who receive sodium fluoride gel treatments or osteoporotic patients who ingest 10-20 mg F once or twice each day. Within the acidic milieu of the stomach, fluoride ions combine with protons to form the weak acid,
hydrofluoric acid (HF) (pK = 3.4). Some products, such as the gels acidified with phosphoric acid, are formulated to have a pH of 3-4, so that about 50% of the fluoride in the container is already in the form of hydrofluoric acid. Compared with fluoride ion, hydrofluoric acid molecule permeates cell membranes and epithelia rapidly. Once then enter the mucosa, where the pH is near neutral, the molecule dissociates to release ionic fluoride and protons.

Several functional and structural dose and time-related changes might be associated with ingestion of fluoride. The fluxes of water, sodium, potassium, protons, and other ions increase sharply; mucus secretion increases, followed by patchy or widespread loss of the mucus layer; hyperemia, edema, and hemorrhage. Surface mucus cells are shed; parietal and chief cells which lie deeper in the gastric pits are injured or shed.

**EFFECTS ON TEETH**

Dental fluorosis results when excessive amounts of fluoride are ingested during the years of tooth formation. Dental fluorosis is characterized by lusterless, opaque white patches in the enamel, which may become stained yellow to dark brown, and in severe forms cause marked pitting and brittleness of teeth. The severity of dental fluorosis is usually ranked according to Dean's classification index as questionable, very mild, mild, moderate, or severe. Recently, the tooth surface index of fluorosis (TSIF) has been used to assess the severity and prevalence of dental fluorosis.

**EFFECTS ON SKELETAL SYSTEM**

A number of mechanisms are involved in the toxicity of fluoride to bone. Fluoride ions are incorporated into bone substituting hydroxyl groups in the carbonate-apatite structure to produce fluorohydroxyapatite, thus altering the mineral structure of the bone. Unlike hydroxyl ions, fluoride ions reside in the plane of calcium ions, resulting in a structure that is electrostatically more stable and structurally more compact. Because bone strength is thought to derive mainly from the interface between collagen and mineral, alteration in mineralization affects bone strength.

Skeletal fluorosis is a crippling pathological condition, which can occur on long term exposure to high levels of fluoride. Impact of fluoride on bone was depicted in Figure 2.

**Effect on bone strength and fractures**

A large number of epidemiological studies have investigated the effect of fluoride intake on bone fractures. The amount of fluoride taken up by bone is inversely related to age. During the growth phase of the skeleton, a relatively high portion of ingested fluoride will be deposited in the skeleton: up to 90% during the first year of life, which gradually decrease to 50% in children > 15 years. There is no clear association of bone fracture with water fluoridation, however fluoride can weaken bone and increase the risk of bone fractures under certain conditions, and a water concentration ≥4 mg fluoride/l will increase the risk of bone fracture compared to 1 mg fluoride/l. Fluoride is present in small amounts in most tissues but is concentrated in the skeleton. It has been found that the ingestion of water-borne fluoride in small amounts (0.7 to 1.5 ppm) reduces dental carries in children. However, the ingestion of massive doses appears to result in significant and profound changes in the growth and mineralization of bone.

**EFFECTS ON BRAIN**

Fluoride is a chemically active ionized element, it may affect oxygen metabolism and induce oxygen free radicals which appears to play a role in diminishing cognitive ability processes such as learning and memory. Moreover, fluoride binds antioxidants in the body such as N-acetyl cysteine (NAC), glutathione (GSH) and other free radical destroying enzymes, triggering oxidative stress that leads to cell damage and even cell apoptosis. Absence of compensatory antioxidant system with the presence of oxidative stress due to increased free radicals plays a great role in initiation of damage of nerve cells membrane especially via increased lipid peroxidation.

After chronic exposure to fluoride, protein content of brain could decrease and DNA content remain stable. Continuous treatment for 7 months with fluoride can produce a decline in the total brain phospholipids content. The main species of phospholipids influenced by fluorosis were phosphatidyl ethanolamine, phosphatidyl choline, and phosphatidyl serine. The fatty acid and aldehyde composition of individual phospholipids classes were unchanged. Chronic exposure of pregnant rats to high concentrations of sodium fluoride has been reported to induce disturbances in the development of brain in offspring of rats. Rats exposed to fluoride showed a number of histopathological changes in the brain, including demyelination, a decrease in the number of Purkinje cells, thickening and disappearance of dendrites, swelling of mitochondria, and dilation of endoplasmic reticulum in neurons.

**Neurobehavioral effects**

Exposure of pregnant female rats to sodium fluoride for 44 days from 8\textsuperscript{th} day of gestation to the end of lactation and weaning of pups showed severe neurobehavioral changes. Lower average body weight gain was observed
Fluoride treatment led to a significant inhibition of fertility rate in males. Fluoride compounds could alter the internal milieu of testis and epididymis causing functional and structural changes. Metabolism and morphology of spermatozoa were also altered. The weights of caput and cauda epididymus in fluoride consumed mice declined significantly, however weights of seminal vesicle and vas deferens were not affected. The motility of cauda epididymal sperm, sperm count in cauda epididymus and cauda epididymal sperm viability (live: dead ratio) decreased significantly. The protein levels, activity of ATPase and levels of sialic acid in the caput, cauda epididymus and vas deferens decreased significantly after sodium fluoride exposure. This decrease in protein levels might be due to impairment of protein metabolism/synthesis. According to Hodge and Smith, sodium fluoride toxicity involves inhibition of enzyme activity, particularly those in which divalent metal cations act as cofactors; the alterations in ATPase activity might be related to the fact that it is either a Ca^{2+} or an Mg^{2+} activated enzyme. Sialic acid is an important constituent of mucopolysaccharides and sialomucoproteins which are essential for the maturation of spermatozoa in epididymis and maintenance of the structural integrity of their membranes. Structural integrity of acrosomal membrane of the sperm is also altered. A significant accumulation of glycogen in the vas deferens, suppression of vas deferens phosphorylase activity, increase in fructose levels in seminal vesicle and altered carbohydrate metabolism mainly by causing inhibition of some key enzymes in glycolysis and tricarboxylic acid cycle were reported after exposure to fluoride.

**EFFECTS ON KIDNEY AND HEPATIC SYSTEM**

Exposure to fluoride can manifest several changes in two key organs involved in metabolism and excretion which are liver and kidney respectively. Impairment of visceral organ function has been demonstrated in fluoride intoxicated animals. Liver is one of the target organs attacked by high amounts of fluoride given by drinking water. As a very active site of metabolism, the liver is especially susceptible to fluoride intoxication. Previous studies, realized on adult rats, have shown that fluoride could produce abnormalities in the liver including degenerative, inflammatory changes, dilatation of sinusoids and hepatic cellular hyperplasia. Abnormal function, metabolism and histopathological changes have been found in liver of sheep, calves, rats, and mice by several research groups.

Kidneys are the primary organs concerned with excretion and retention of fluoride after chronic industrial
exposure. Fluoride toxicity to nephrons causes pathological changes in the glomeruli and in the proximal, distal, and collecting tubules of experimental animals. Its effects on glomerular function are less severe than proximal tubule. Other manifestations of the toxic effect of fluoride include its effect on kidney of suckling mice whose mothers received fluoride was also reported.

**EFFECTS ON THYROID FUNCTION**

Fluoride can induce structural changes and dysfunctions in the thyroid gland. The thyroid gland has a strong capacity for absorbing and accumulating fluoride. Fluoride can directly injure the structure of the thyroid follicle, induce cytoplasm reduction, karyopycnosis of follicular epithelial cells, reduce the number of microvilli on the cristae of epithelial cells, and lead to swelling vacuoles in follicular epithelial cells of the thyroid gland. Also, fluoride disturbs the synthesis and secretion of thyroid hormone, interferes with the activity of enzymes that catalyze the conversion of thyroxine (T4) into the active thyroid hormone triiodothyronine (T3) and inactive metabolites, thereby leading to perturbation of circulating thyroid hormone levels. Furthermore, ingesting excess fluoride stresses the functional status of the hypothalamus-pituitary-thyroid system, thus adversely affecting the synthesis of DNA and RNA in thyroid cells. Moreover, both iodine and fluorine has antagonistic effects on the thyroid gland leading to the use of fluoride therapy for hyperthyroidism.

Thyroid hormones are necessary for maturation in the postnatal animal, particularly for the central and peripheral nervous systems and the skeleton. Maturation in the rat cerebellar cortex is markedly affected by thyroid hormone levels. Hypothyroidism and anemia have occurred not only with anti thyroid medications but also with fluorine. Thyroid deficiency in early life has a marked influence on the functional development of the central nervous system and is accompanied by significant effects on the structural and biochemical maturation of the cerebellum. As a halogen, fluorine is related chemically to iodine and is very much reactive chemically than iodine. Although thyroid function and structure are purported to be unaffected by 1 ppm fluoride in drinking water, adverse changes occur with higher intakes in endemic fluorosis areas or with fluoride treatments. Increased dietary fluoride has resulted in thyroid enlargement reduced thyroid adenylate cyclase, decreased blood thyroxine (T4) and triiodothyronine (T3) levels. Yu found a decreased serum T4 and an increased TSH level in the residents of an endemic fluorosis area where there was an adequate iodine intake.

**EFFECTS ON OTHER PARAMETERS**

Studies have shown that fluoride can induce excessive production of oxygen free radicals leading to the decrease in biological activities of some substances, such as catalase (CAT), superoxide dismutase (SOD), xanthine oxidase (XOD), and glutathione peroxidase (GSH-Px) which play important roles in anti oxidation and eliminating free radicals. Secondly, fluoride can also disturb the metabolism of proteins. It is indicated that fluoride can impair the activities of a series of enzymes such as alkaline phosphatases; cholinesterase and adenylate cyclase. Fluoride can interfere with the metabolism of carbohydrate, lipid and nucleic acids, injure immune system, and damage various parts of the body.

**CONCLUSION**

The presence of fluoride in drinking water could have deleterious consequences on the physiological system. Skeletal and dental toxicity was most common because of fluorides, however soft tissues could also be afflicted with damage by fluoride. Care and precaution should be advocated in growing children consuming fluoride containing drinking water in order to minimize fluoride related disabilities.

**REFERENCES**


23. Chinoy NJ, Sharma A. Amelioration of fluoride toxicity by vitamin E and D in reproductive functions of male mice. fluoride 1998; 31:203-216


### Different Forms of Fluoride

- **Sodium Fluoride**: Highly toxic form of fluoride, soluble in water hence major source is drinking water.
- **Calcium Fluoride**: Very less toxic compared to other forms of fluoride as it is very slightly soluble in water as well as in HCl of gastric pH.
- **Aluminum Fluoride**: Not classified as hazardous, but it may cause irritation of respiratory tract and eyes.
- **Phosphorus Fluoride**: Widely used in refrigerant industry, etching the glass of light bulbs.
- **Magnesium Fluoride**: Moderately toxic by ingestion. May cause gastrointestinal irritation, severe nausea, vomiting, diarrhea, dehydration and thirst, muscle weakness, headache, convulsions and central nervous system depression.
- **Hydrofluoric Acid**: Used for industrial purposes and is very corrosive acid. It causes severe damage on dermal exposure but is initially painless.
- **Sulfuric Fluoride**: Insecticide used to fumigate closed structures which is moderately toxic and shows neurotoxicity after long term exposure.
- **Sodium Monofluorophosphate**: Used extensively in air conditioning and refrigeration.
- **Sodium Monofluorophosphate (NaF)**: Used in dentifrices and mouth rinses. It is less irritant than sodium fluoride as phosphates are needed to break the covalent bond between Fluorine and phosphorus which has limited activity in gastric mucosa. The LD₅₀ in rats is 0.9 g/kg.

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**Figure 2** Impact of fluoride on bone

**Figure 3** Forms of fluonides and their uses