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FLUORIDE: AN EVALUATION AND EVIDENCE ON HUMAN DEVELOPMENTAL METABOLIC AND NEUROLOGICAL CHANGES - EPIDEMIOLOGICAL STUDY

Biological Science

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ABSTRACT

Fluoride is widely present in our surroundings in a variety of forms and has the potential to adversely affect the biological environment and human health. For teeth and bones to remain healthy, fluoride is essential. Although too much fluoride might harm an animal's body, it is necessary for animals to grow and develop healthily. The majority of the state's groundwater is either salty or contains significant levels of fluoride and nitrates. The neurological system is primarily affected by fluoride's harmful effects on the body. Numerous research conducted recently have demonstrated that fluoride might be harmful to macrophages and other immune system components. The kidney, liver, and heart are the delicate tissues that are most vulnerable to fluoride poisoning. Fluoride toxicity researchers have recently become interested in free radicals and oxidative stress. Cognitive decline, compromised neuronal and cerebrovascular integrity, and metabolic abnormalities are all examples of fluoride's neurotoxicity. The toxicity of fluoride large quantities of certain fluoride salts can be harmful to the skin or eyes, and soluble fluoride salts are toxic in large concentrations. Age range: 07–14 years old In comparison with the control participants, the fluoride content in the serum was considerably ($p<0.001$) higher in the severe subjects (519%), moderate subjects (320%), and mild subjects (140%). Between the ages of 15 and 45, the blood fluoride content was considerably ($p<0.001$) higher in the severe group (5172%), moderate group (268%), and mild group (165%). topics under control. Age range: 46–75 years old When compared to the control subjects, the severe subjects had significantly ($p<0.001$) higher serum fluoride concentrations (694%), followed by moderate subjects (432%) and mild subjects (240%).

KEYWORDS

Dental, skeletal, non-skeletal, sodium fluoride, fluoride, toxicity, fluorosis, and environment.

INTRODUCTION –

Fluoride is widely present in our surroundings in a variety of forms and has the potential to seriously impair both human health and the environment ecological Worldwide, there have been several reports of fluorosis instances. Fluorine pollution of soil is a severe problem, particularly in China., where it is increasingly having a detrimental effect on the environment and human health. Animals need fluoride for healthy growth and development, even though too much of it can be harmful to the body. Dental fluorosis, hypertension, skeletal fluorosis, reproductive disorders, and dementia are the typical indicators, according to a number of phenomena. Fluorosis. Excessive fluoride deposition can cause sleeplessness, somnolence, and other symptoms. Fluoride mostly damages teeth, bones, and the central nervous system by traveling across the blood-brain barrier. Excessive fluoride consumption has been shown to damage the kidney, liver, brain, and ovaries, among other organs. The stomach and intestines receive the majority of fluoride from the environment, which is then deposited in soft tissue and bone through the cell membrane and damages these tissues. The liver is the primary site of deposition, while the kidney is the primary site of excretion. Long-term fluoride exposure causes fluoride to build up in liver tissue, alters the expression of cyclooxygenase and the activity of antioxidant enzymes, severely damages hepatocyte ultrastructure, causes major pathological alterations in liver tissue, and upsets the body's equilibrium. Symptoms of excessive fluoride deposition include somnolence and insomnia. Because fluoride crosses the blood-brain barrier, it mostly harms teeth, bones, and the central nervous system. It has been demonstrated that consuming too much fluoride harms the kidney, liver, brain, and ovaries, among other organs. The net balance of glucose intake from circulation, glucose metabolism to lactate and CO2, and glucose transit back to circulation is represented by the brain's glucose level.

Fluoride In Rajasthan

India's northwest contains the state of Rajasthan. Despite being the largest state in the nation, it only boasts 1% of the nation's water resources. The climate and geography of the state are quite harsh. Both the amount and quality of water are issues in Rajasthan. Rajasthan's water availability and use situation is quite dire. The majority of the state's groundwater is either salty or contains significant levels of fluoride and nitrates. Numerous rocks are the source of fluoride in Rajasthan's drinking water. These stony belts stretch from Gujarat to Delhi. According to geology, there is a band beneath the Aravalli range that runs from South-East Rajasthan and from Pinch Mahal, Gujarat, to Gurgaon, Haryana. and traveling through the fluorspar, cryolite, and fluorapatite-rich region of south-east Rajasthan. This fluorotic belt is known as Banka-Patty because the majority of its residents have skeletal abnormalities. According to Rajasthan's geological rock distribution, the state's eastern and southeast regions are largely occupied by ores that produce fluoride. Additionally, Rajasthan has mica mines with abundant groundwater. Fluoride Millions of people in Rajasthan have been rendered disabled as a result of swallowing excessive amounts of fluoride, making it the most impacted state in India. Fluoride-prone locations have been identified in all 33 districts.

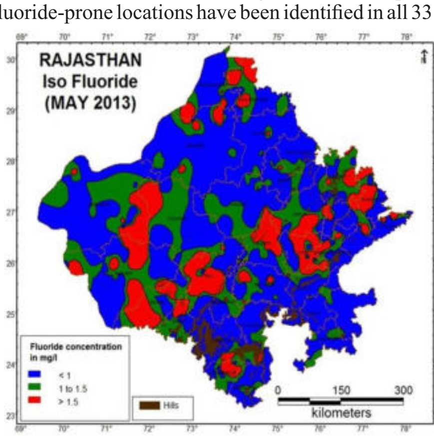


Fig.1: Rajasthan's fluoride distribution map

Fluoride In India:

In India, fluorosis has existed for almost 85 years. In British India, the Madras Presidency and the Nellore district of Andhra Pradesh were found to have high rates of fluorosis and excess fluoride in the groundwater. High fluoride levels have been reported in 18 states and one territory, suggesting that endemic fluorosis has emerged as a public health concern in the country. Millions of people who reside in places with high fluoride levels are at risk for fluorosis. Industrial fluorosis is also observed in several areas of Gujarat and Uttar Pradesh. According to the (BIS) Bureau of Indian Standards, the lower the fluoride content in water, the better. The ideal limit is 1 ppm (parts per million) or 1 mg/L. The BIS guideline of 1.0 mg/L is the upper limit because fluorosis has been known to occur in India even at 1.5 mg/L of fluoride. There are now 48 mg/L of fluoride documented in Indian water sources; however, there may be unusual sources with even greater fluoride concentrations that are not used for everyday purposes.

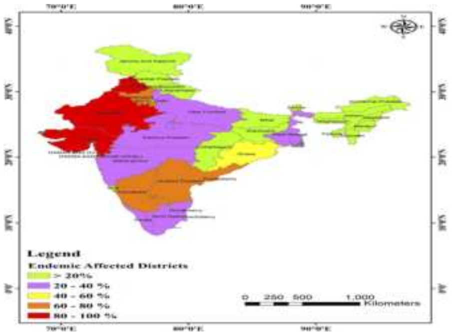


Fig.2: A map of India that displays the distribution of fluoride (in parts per million) across the various states and union territories. Published scientific reports served as the basis for the preparation or modification of this map.

General Effects Of Fluoride On The Body:

The detrimental effects of fluoride on the body mostly affect the neurological system. Neurodegenerative illnesses may develop more quickly as a result of long-term exposure, which alters the brain by reducing neurons and losing grey matter. Additionally, it creates problems with concentrate, sleep, and memory. Children are particularly at danger from fluoride because it can pass through the blood-brain and blood-placenta barriers, which could cause cognitive development delays and later learning challenges.It has also been demonstrated that too much fluoride damages other human organs, such as the stomach, liver, and testicles, by causing inflammation and oxidative stress. The limited research that has been published so far indicates that fluoride compounds negatively impact the endocrine system and can eventually cause significant impairments to the body's metabolism.

Fluoride Toxicity –

Large quantities of certain fluoride salts can be harmful to the skin or eyes, and soluble fluoride salts are toxic in large concentrations. They are absorbed by the stomach and intestines and eliminated through urine, just like the majority of soluble substances. It is commonly known that trace elements, which function as cofactors and are crucial for numerous metabolic processes, are both necessary and advantageous to human health at trace amounts. However, going over their allowed intake is proven to be harmful and negatively impact the body's overall metabolism. One such trace element that is frequently present in soil, earth, and water is fluoride. A small amount of fluoride (0.3–1.0 mg/L) in drinking water is known to help prevent tooth cavities and treat osteoporosis. However, it is well recognized that prolonged exposure to high fluoride levels (1.5 mg/L) in drinking water damages tooth enamel and eventually causes skeletal problems that culminate in the debilitating disease known as fluorosis.

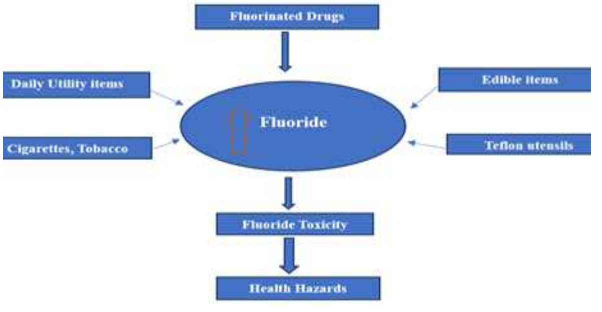


Fig.3: fluoride toxicity

Disease Types and Fluoride-Related Symptoms:

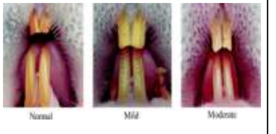
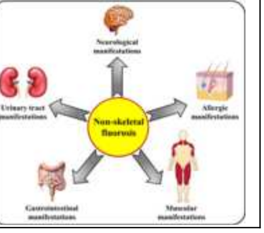
1	Diseases	Symptoms	Images
2	Skeletal fluorosis	severe joint and back bone pain and stiffness. Severe hip pain and stiffness X-ray: In addition to ligament calcification, there is increased bone density and girth/thickening. Immobility	
3	Dental flu orosis	The teeth's natural lustre or shine fades. Initially chalky white, it eventually turns yellow, brown, or black. tiny surface holes or pits. Edentulous.	
4	Non-skeletal fluorosis	Gastrointestinal issues, loss of appetite, stomach pain, constipation with sporadic diarrhoea, weakness in the muscles, neurological symptoms, stillbirths or abortions, male infertility, cardiac issues, etc.	

Fig.4: Types of Diseases and Symptoms Associated with Fluoride

Skeletal Fluorosis:

(SF) Skeletal fluorosis, a long-term metabolic bone condition brought on by consuming fluoride ions or, less commonly, inhalation, is seen in areas with naturally high fluoride levels. Asymptomatic SF is often discovered by accident during radiological testing. Anticondensation, osteopenia, limited mobility, and generalized skeletal discomfort are some of the manifestations that may result from the ossification of several ligaments and interosseous membranes.

In some regions of the world, especially India, where it was first discovered in the 1930s, SF is a widespread problem. Additionally, it can occur sporadically in almost every nation where phosphatic rock is abundant in the ground or as a result of industrial exposure.

Dental Fluorosis

There has always been a trade-off between the risk of fluorosis and the protection against dental cavities when using fluoride to improve oral health. A small percentage of people who consume fluoride during the tooth formation period, which is the first few years of life, suffer dental fluorosis, a condition of enamel development. One The most frequent side effect of using fluoride to prevent dental cavities is dental fluorosis. Dental fluorosis is significant for public health because it serves as a population indication of young children's exposure to fluoride, or the canary in the coalmine. The following factors make dental fluorosis a serious problem for oral health: (i) dental fluorosis has recently become a prominent side effect of fluoride use in scientific research; (ii) dental fluorosis is now commonly included in public evaluations of the safety of fluoride use; and (iii) recommendations regarding fluoride use should be based on data demonstrating a risk-benefit trade-off between the risk of developing fluorosis and the preventive benefit against dental caries.

Non- skeletal fluorosis:

Refers to the harmful consequences that excessive fluoride exposure has on tissues and organs besides bones and teeth. Non-skeletal fluorosis affects soft tissues and physiological systems, frequently presenting as a variety of systemic health problems, whereas skeletal fluorosis affects the bones and joints. It usually happens in areas where water drinking contains high amounts of fluoride or as a result of various exposures at work or in the environment. Fluoride exposure can lead to non-skeletal fluorosis, affecting various organs and tissues beyond the skeletal system. Chronic fluoride toxicity can cause multiple organ damages, including neurological impairment, kidney dysfunction, and muscle impairment.

Fluoride standard Individuals' permissible limitations as determined by the recommended regulatory body:

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Table-1: Standard fluoride Permissible limits for an individual's given by recommended regulatory Authority

Name of the organization	Desirable limit (mg/L)
Indian Standards Bureau (BIS)	0.6-1.2
Medical Research Council of India (ICMR)	1.0
The Government of India's Committee on Public Health Engineering Manual and Code of Practice	1.0
International Standards for Drinking Water, World Health Organization	1.5

Consumable intake limit of Fluoride Content in Food items:

Table-2: Consumable intake limit of Fluoride Content in Food items

Food Item	Fluoride (mg/kg)	Food Item	Fluoride (mg/kg)
Cereals		Fruits	
Wheat	4.7	Banana	2.9
Rice	5.8	Mango	3.3
Maize	5.7	Apple	5.6
Gram	2.6	Tea	60-112
Soyabean	5.0	Coconut Water	0.32-0.7
Cabbage	3.4	Coriander	2.5
Tomato	3.5	Garlic	5.0
Cucumber	4.1	Ginger	2.0
Lady Finger	4.0	Turmeric	3.4

Environmental Fluoride:

The diatomic gas fluorine (F_2) has a greenish hue. Except in certain industrial operations, fluorine is seldom found in its elemental gaseous state due to its extreme reactivity. Cryolite, Na_3AlF_6, Sellaite, fluorspar, CaF_2, and fluorapatite, $3Ca_3(PO_4)_2\,Ca(F,Cl_2)$ are notable forms of fluoride. It occurs in sedimentary rocks as fluorspar and in igneous rocks as cryolite. Water hardly dissolves these fluoride-containing minerals. As a result, fluorides will only be found in groundwater when favourable conditions are met. Additionally, it can be found in mica, seawater (0.8–1.4 ppm), and numerous drinking water sources. The information that is currently available makes it clear that a specific amount of fluorine is necessary for both the normal mineralization process in hard tissues and the development of tooth enamel that is resistant to cavities. Both covalent and electrovalent molecules are used to metabolize the element. By making the apatite crystals larger and less soluble, low fluoride concentrations stabilize the skeletal systems. Approximately 95% of fluoride in the body is deposited in hard tissues, and even after other bone has been calcified, it still remains deposited in these structures. The levels of the constituents (Ca, P, Mg, CO_3, and citrate) are stable. The degree to which fluorine is integrated into the skeleton depends in large part on age. After the age of thirty or so, the absorption in dental enamel virtually stops.

Fluoride Prevalence In Indian Ground And River Waters:

Fluoride levels in numerous rivers that traverse over six Indian states have been found to range from 0.1 to 12.0 parts per million. Many people in A.P., Rajasthan Jaipur, Punjab and Haryana, Maharashtra, Tamil Nadu, Karnataka, Madhya Pradesh, Gujarat, and Uttar Pradesh have also reported the presence of fluoride-containing waterways.

Fluoride Levels Were Calculated For Several Age Groups:

Fluoride In Serum: Data are shown for the estimated serum fluoride levels in various age groups.

Age Range 07–14 Years Old:

In comparison with the control participants, the fluoride content in the serum was considerably ($p<0.001$) higher in the severe subjects (519%), moderate subjects (320%), and mild subjects (140%). Conversely, there was a 47% increase in fluoride concentration in the severe group compared to the moderate group, and a 158% increase in the moderate group compared to the mild group.

Age Range 15–45 Years Old:

Serum fluoride levels were substantially ($p<0.001$) higher in severe participants (5172%) than in moderate subjects (268%) and mild subjects (165%) than in the control group. Conversely, the fluoride concentrations in the severe (132%) and moderate (38%) groups were higher than those in the mild group, and the severe group was 68% higher than the moderate group.

Age Range 46–75 Years Old:

When compared to the control subjects, the severe subjects had significantly ($p<0.001$) higher serum fluoride concentrations (694%), followed by moderate subjects (432%) and mild subjects (240%). Conversely, there was a 49% increase in fluoride concentration in the severe group compared to the moderate group, and a 134% increase in the moderate group compared to the mild group.

Fluoride Sources For Exposure In Plants, Animals, And Humans:

Water, food, air, medications, and cosmetics are the main places where people might be exposed to fluoride. Approximately 60% of fluoride exposure is thought to come from drinking water. Because fluoride has an affinity for calcium phosphate ($Ca_3(PO_4)_2$) in bones, 96–99% of it combines with bones. Other types of fluoride are somewhat less harmful. Foods that are good sources of fluoride for human consumption include tea, fluoridated toothpaste, soil-grown fluoride-rich plants and vegetables, pan, supari, tobacco, green garlic, onion, cabbage, soybeans, carrot, corn, potato, baking powder, egg, and cow liver and kidney. The long-term adverse effects of fluoride have been connected to the long-term use of a number of drugs, including mouthwash, sodium fluoride (NaF) for osteoporosis, and in-fluoric acid for rheumatoid arthritis. The use of fluorides in industry often results in occupational exposure. For instance, inorganic fluoride compounds are used in the production of aluminium and phosphate fertilizers. When cattle graze close to fluoride sources, such as ceramic pebbles, phosphatic fertilizer firms, and aluminium producers, fluorosis sometimes develops. Teeth discoloration, mottling, and abrasion, elevated fluoride levels in bones and urine, reduced milk production, and lameness are the harmful effects. Animals grow sluggish. The soil determines how much fluoride is in the water. Fluoride levels in soft water are low, but they can be high in hard water. The fluoride concentration of crop plants cultivated in agricultural and non-industrial areas with high fluoride soils reached 300 parts per million. Some crops, cottonseed, tea, and fish meal contain comparatively high levels of fluoride. Food-based fluoride is organically bonded and non-toxic. Drugs that contain fluoride that the body can metabolize include anti-carcinogenic medications, medications used to treat osteoporosis and associated metabolic disorders, certain aesthetic medications, fluoridated corticosteroids, and dentine obtundents.

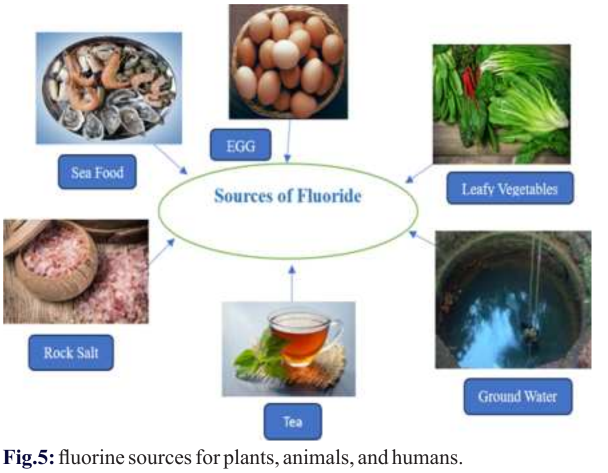

Fig.5: fluorine sources for plants, animals, and humans.

Toxic Effects Of Fluoride On Domestic Animals And People:

Tooth And Bone Toxicity:

For human teeth and bones to be healthy, fluoride is required.Dental cavities are avoided, enamel remineralization is encouraged, and bone density is increased with adequate fluoride administration. and osteoporosis. On the other hand, dental fluorosis can result from consuming too much fluoride. An early sign of Exposure to continuously high fluoride concentrations causes dental fluorosis, a discoloration of the enamel that can lead to discrete or ag aggregated pitting. A study conducted in the southern Rajasthani districts of Bansari, Dungarpur, and Udaipur found that 36% of adults and over 21% of children had dental fluorosis at drinking water fluoride levels of 1.5 ppm. The highest prevalence rates of dental fluorosis (77.1%) were found in the 17–22 age range. Additionally, dental fluorosis symptoms were present in all 200 participants in a study of individuals aged 7 to 40 in rural Ethiopian Rift settlements, where water fluoride levels range from 7.8 to 18 mg/L. It's interesting to note that drinking milk helped to lessen the severity of symptoms in this study. Limb motor dysfunction, restricted joint movement, and chronic, ongoing joint discomfort are further clinical signs of fluorosis. Patients who suffer from severe health issues like paralysis find their lives considerably more difficult as a result of these symptoms, especially in places like India and other nations. Patients' and their families' physical and mental health may suffer as a result of fluorosis, which is seen as a public social health issue.

Neurological Effect Of Fluoride Toxicity-

Given its ability to cross the blood–brain barrier, fluoride may pose a serious threat to the mammalian neurological system. Because fluoride inhibits numerous important neural enzymes and increases lipid peroxidation, excessive fluoride consumption might cause metabolic problems unique to the brain. High fluoride exposure levels in bone can also seriously harm other tissues, including nerves. Fluoride may directly affect brain activity, as Cheng et al. demonstrated in rats that it can directly affect myelin, neurons, and neurotransmitters. Newborns whose mothers consumed large amounts of fluoride during pregnancy exhibited slower neonatal neurodevelopment than newborns who were not exposed to high levels of fluoride, according to a study describing the effects of fluoride intake during pregnancy on neonatal behavioural neurodevelopment. Additionally, research revealed that children who lived in high-fluoride areas scored much lower on IQ tests than those who lived in low-fluoride areas. All things considered; it seems that too much fluoride could seriously impair neurodevelopment.

Immune System Toxicity –

Fluoride may be detrimental to macrophages and other immune system components, according to a number of recent studies. The transcription factor nucleic acid-kappa B (NF-κB) is crucial for regulating gene expression during immunological and inflammatory reactions. Mouse phagocytes treated with high doses of NaF altered the expression levels of nitric oxide H. Zuo et al. Life S synthase and interleukin-1 beta (IL-1β) in an NF-kB-dependent manner, which resulted in decreased cell adhesion and impaired phage cytosis.

Toxicity On Abdominal System-

The soft tissues most vulnerable to fluoride toxicity include the kidney, liver, and heart. Prolonged fluoride exposure causes histological and functional abnormalities in all three organs. Chronic kidney disease is more likely to occur in those who regularly consume fluoride through their diet and water. Mice treated to high doses of fluoride have lower blood glutathione peroxidase and superoxide dismutase activity, raised malondialdehyde levels, increased urine fluoride concentrations, and renal cell apoptosis, all of which suggest that excessive fluoride ingestion may harm the kidneys. Additionally, it has been documented that NaF raises ROS production and increases NF-kB expression in the kidneys and heart, which results in hypertension. The survival of mature liver progenitor cells throughout embryonic development depends on the expression of the Hedgehog (HH) signalling pathway, a signalling system involved in both embryonic development and differentiation. Numerous studies have demonstrated that the pathophysiology of a number of liver illnesses is significantly influenced by aberrant activation of HH signalling, particularly Sonic hedgehog (Shh). Studies have demonstrated that rats exposed to fluoride exhibit increased activity of liver-specific alanine amino transferase and aspartate aminotransferase, altered liver architecture, decreased total protein and albumin content, and abnormal activation of the Shh signalling pathway. Thus, prolonged fluorosis-induced liver damage may include the Shh signalling system.

Oxidative Stress-

Researchers studying fluoride toxicity have recently developed an interest in oxidative stress and free radicals. Curnutte and Babi (1975) examined the impact of anaerobic conditions and inhibitors of superoxide anion ($O2^-$) production in human polymorphonuclear leukocytes. When compared to untreated cells, they found that the PMN and NaF combination increased O2 generation by 20 times. The inner mitochondrial membrane contains the antioxidant uncoupling protein-2 (UCP2), which is a member of the mitochondrial anion transporter superfamily. discovered that when mature rat incisors are exposed to F-treatment, UCP2 is up-regulated. Under oxidative stress, UCP2 can be activated by ROS and reduces ROS generation and mitochondrial superoxide emission by negatively regulating ATP synthesis and mitochondrial membrane potential. Here, the scientists deduced that UCP2 up-regulation may attenuate ATP generation, which could lead to dental fluorosis by preventing mature ameloblasts from reabsorbing the enamel matrix proteins required for the creation of hardened adult enamel. These findings imply that dental fluorosis is significantly influenced by the ROS–UCP2 pathway. It's interesting to note that despite a great deal of recent research, the physiological role of UCP2 is still unknown. It is increasingly clear that UCP2 has tissue- and organ-specific effects and is linked to neurodegenerative, liver, cardiac, and diabetic disorders.

Fluoride-induced Cognitive Decline:

Cognitive decline, compromised neuronal and cerebrovascular integrity, and metabolic abnormalities are all examples of fluoride's neurotoxicity. The harmful effects of fluoride are thought to be largely caused by lipid peroxidation, the production of free radicals, and compromised antioxidant defence mechanisms. Increased transit in the bloodstream and probably across the blood-brain barrier are signs of fluoride exposure. Fluoride toxicity in the brain could be caused by lipid peroxidation, excitotoxicity, or an increase in free radical generation. Excitotoxicity has been shown to harm dendrites and synaptic connections, which causes neurons to die. The brain is especially susceptible to oxidative stress due to the presence of ions and metals, low antioxidant levels, and high quantities of polyunsaturated fatty acids (PUFA) (Muthu & Meenakshi, 2015).Fluoride toxicity is a hot topic for research and discussion because of its widespread availability and toxicity at all stages of life. Furthermore, its presence in soft tissues, especially the brain, in adults and the elderly is poorly understood.

CONCLUSIONS.

The dosage and test organs affected the body's reaction to fluoride toxicity. It should be mentioned that although the trials employed varying doses of fluoride, human exposure to fluoride in drinking water rarely surpasses 50 mg/L. Fluorosis is endemic in the state known as the Museum of Minerals. High temperatures and mineral rocks are ideal for the formation of fluoride. Agriculture uses more water because of our agrarian economy, which lowers the water table, increases the amount of fluoride in groundwater, and widens the Dark Zone. The effects of fluoride poisoning on living things have recently piqued the interest of toxicologists. Numerous studies on the toxicity of fluoride in different animals have employed high fluoride levels in drinking water. The development of the brain, thyroid, chromosomes, liver, kidney, heart, lungs, neurological system, and reproductive abilities have all been observed to exhibit a number of pathological changes. Changes have also been observed in plants growing in areas impacted by fluoride pollution. The high fluoride levels and the enhanced send fluoride concentration were shown to be significantly correlated. Seductive abilities were negatively impacted by moderate to severe blood fluoride levels in all age groups. The IQs of the fluoride-exposed children were noticeably higher than those of the control group. GHQ and MMSE also revealed poorer behavioural performance in the group that had been exposed to high levels of fluoride. The neurodegenerative process and compromised brain function may be reflected in the elevated fluoride accumulation in the brain serum. The current study's findings indicate that moderate stress and changes in trace metal analysis occur in individuals of all ages exposed to fluoride. Since there isn't a suitable source of diminishing water, these changes could lead to pathophysiological activities. High fluoride levels in drinking water (bore well water) and related health issues are linked to cognitive decline in children, adults, and the elderly. There is a direct correlation between elevated serum fluoride levels and acetylcholinesterase.

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