



Review article

Ground water fluoride induced neurological changes in brain: a promising reviewSathasivam Rajkumar¹, Swaminathan Gomathi^{2*}, Chinnadurai Kannan¹, Byran Gowramma², Ramanathan Sambathkumar¹

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ABSTRACT

Fluoride is now found in many sections of the world's groundwater. Across the globe, more than 25 countries have found evidence linking fluoride, a single ion, to health concerns. Although a highest limit of fluoride in groundwater has been set by the World Health Organization, it has been found to be exceeded in a number of nations. According to WHO estimates from 1984, more than 260 million people drank water with more than 1 mg/L of fluoride. Tamilnadu is one of the Indian states where fluoride contamination has been discovered. Several organs of the body, including the brain, have been found to be damaged by long-term fluoride exposure. Fluoride produces free radicals, increases lipid peroxidation, depletes antioxidants, inhibits essential enzymes in biochemical activities, lowers energy production, and restricts protein synthesis. The primary goal of this paper is to explain how fluoride might cause neurotoxicity in the brain.

Keywords: Fluoride, Oxidative Stress, Ground water, Neurotoxicity, Anti-oxidants.

Received – 19/08/2021, Reviewed - 27/10/2021, Revised/ Accepted- 21/11/2021

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INTRODUCTION

Groundwater is the most important resource for a wide range of purposes in many parts of the world. To use underground for consumption and other home needs, such as cooking, no physiochemical testing is necessary. There are numerous health issues that might result from a bad habit like this one. Although this method cannot be avoided in many sections of underdeveloped nations, a lack of clean piped water distribution infrastructure does not allow it. It is quite concerning when groundwater becomes unusable due to abnormally low or excessive concentrations of specific ions.^[1]

The much more electronegative of the halogens is fluorine. Several other elements must be present for fluoride to develop. Living organisms are exposed to fluoride through their consumption of food and water. Hydrogen fluoride, calcium fluoride, sulphur hexafluoride, sodium fluoride, and silico fluoride are the most major inorganic fluorides that threaten the ecosystem because of their composition. Air, top soil, and water all contain it. As a gas, fluorides are released into the atmosphere. It is possible to distribute fluorides over great distances by wind before they are deposited or diluted in water. Fluorides, apart from sulphur hexafluoride (SF₆), are generally incapable of surviving in the environment for lengthy periods of time.

The far more electronegative element and the major components of the halide complex are fluorine. Fluoride is formed

when it reacts with several other elements. The major source of fluoride exposure for living creatures is through their consumption of water and food. Hydrogen fluoride, calcium fluoride, sulphur hexafluoride, sodium fluoride, and silico fluoride are the most important inorganic fluorides that have harmful impacts on the ecosystem based on the composition emitted. It can be found in the air, top soil, and water. Fluorides are discharged into the atmosphere as a gas. Fluorides can be dispersed over long distances by wind before being deposited on the surface of the earth or diluted with water. Apart from sulphur hexafluoride (SF₆), which has a residual time in the atmospheric of several thousand years, fluorides are usually unable of persisting in the environment for a prolonged duration.^[2]

In over 25 nations, fluoride is associated to a wide range of health issues. Globally, fluoride levels in groundwater have been found to go beyond the World Health Organization's (WHO) permitted limit is 1.5 mg/L. In 1984, the WHO predicted that 260 million people all over the world were wasting water that contained and over 1 mg/L inorganic fluoride.^[2] Researchers from India, Iran, China, Pakistan, the Turkish Republic of South Africa (Southern Algeria), Sri Lanka, Japan, Kenya, Ghana, and Norway have all discovered increased fluoride concentration in underground water. An additional possible factor of fluoride consumption, in contrast to

potable water, includes meals, alcoholic beverages, and orthodontic instruments such as toothpaste, and many others.^{[3],[4],[5]}

In order to maintain good health, fluoride is required. While it is widely accepted level of fluoride (1.0 mg/L) in consumption water can help reduce the incidence of dental caries, especially in children^[6], higher levels of fluoride in the body be able to show the way to a multiplicity of wellbeing issues, together with nervous system disruption^[7], decreased fertility^[8], cognitive dysfunction in children^[9], urinary bladder disease^[10], and skeletal and dental fluorosis in children and adolescents.^[11] As a result, you may have excruciating pain in your lower back.^[12] Dental fluorosis is thought to be caused by water with a fluoride level of at least 0.9 mg/L in 37 percent of persons who have it. Various researches looked into the link between fluoride in underground water and bone diseases (osteosarcoma) in teenagers and young adults.^[13] Fluoridated water has been reported to cause a rise in plasma Endothelin-1 (ET-1) concentration as well as hypertensive in adults.^[14] As per a survey, fluorine in water supply is connected to an elevated risk of atherosclerosis in the carotid arteries in elderly.^[15]

India's fluoride exposure

Fluoride levels have been reported to be excessive in groundwater sources in a few states in India. In many parts of India's arid and semi-arid regions, groundwater contamination with fluoride is a common problem. Fluoride levels are highest in Rajasthan, Andhra Pradesh, Telangana, Tamilnadu, West Bengal, and Gujarat. Over a lengthy period of time, fluoridated water can induce fluorosis in both people and animals. 66 million Indians are at threat due to fluoride-contaminated water.^[16] Elevated fluoride levels in ground water, a considerable number of rural people are at danger of getting fluorosis, which affects around 90% of the country's population.

Fluoride contamination Tamilnadu

Water tests conducted in the western part of Tamil Nadu exhibited strong fluoride levels, which did not meet standards. Residents of the area are suffering from teeth fluorosis because of high fluoride concentrations found in groundwater sources that are mostly used for drinking. Fluoride levels in the ground rose during the monsoon season rainfall, compared to previous months. Ten districts in the state of Tamilnadu have elevated level of fluoride in their ingestion water. Coimbatore and, Trichy are the second, third most fluoride-rich districts in Tamil Nadu after Dharmapuri and Krishnagiri respectively. Dindukal and Chidambaram round out the top five. Fluoride levels are low in the districts of Thirunelveli, Pudukottai, North Arcot, and Ramnad.^[17]

A high of 1.56 ppm of fluoride was found in Puliampatti, 1.90 ppm in Kadamban Kurichi and 1.31 ppm in Rangampalayam villages in the Coimbatore, Tiruppur, Erode, Dindigul, Karur and Namakkal districts' groundwater respectively. After observing the

spatial variation of fluoride content in the groundwater in Thalavadi and Sathyamangalam as well as Karamadai and Annur, the challenging groundwater class was established in Thalavadi and Sathyamangalam as well as Karamadai and Annur and Gobichettipalayam as well as Anthiyur and Bhavani as well as Bhavani as well as Kulathur as well as Erode as well as Thiruchengode as well as Kodaikanal as well as Palan as well.^[17]

Five taluks make up Namakkal, which is located in the state of Tamil Nadu. There are 15 blocks in each taluk that are further subdivided into 391 villages. Phreatic aquifer water in Namakkal district is often colourless, odourless, and alkaline. Fluoride rates greater than that of the surface and groundwater level of 1.5 mg/L were discovered in 30% of tests in various sections of Namakkal. Fluoride levels are elevated in regions like Venandur, Udaiyarpalayam and so on.^[18]

Fluoride oxidative stress inducer

Oxidative stress and changes in antioxidant levels have been linked to fluoride exposure in both humans and animals. In neurodegeneration, oxidative stress and excitotoxicity are the two primary processes that cause the majority of cell damage and destruction. Oxidative stress arises when the brain's regular antioxidant defence mechanisms are overwhelmed by the creation of strong oxidising chemicals such as reactive oxygen and reactive nitrogen species (ROS and RNS).^[19]

H₂O₂ and superoxide (•O₂) are well-known ROS. Nitric oxide (•NO) and, peroxy nitrite (ONOO-) are two of the most common RNS. To put it simply, when antioxidant defences are exhausted or the reaction rates of reactive species outpace those for antioxidative defence mechanisms, oxidative stress occurs.^{[20],[21]} An increase in O₂ generation (anion superoxide) was observed after fluoride exposure;^[22] this was followed by a decrease in O₂ concentration. The fluoride may also interact with •O₂ to form ONOO- and through thiols, protein metal centre, to produce the conjugates of nitrosyl, as well as boost NO production.^[23] As a result, ROS production and ER stress have been found to be caused by the disruption of disulfide bonds, which can lead to the addition of degraded proteins to the endoplasmic reticulum (ER).

Studies in animals, particularly those living in fluorosis-prone areas, have shown that fluoride interaction produces oxidative stress in several cell types and tissues such as those found in the brain and liver, as well as kidney and lung tissue and testes.^[24] As key pathological regulators, ROS have been connected to a wide variety of illnesses. The enhanced production of ROS via lipid peroxidation is reflection to be the cause of toxicity of a wide variety of substances.^[25] The connection among fluoride water and, free radicals has been studied by a number of scientists.^{[25],[26]} From both human and animal studies, chronic fluoride poisoning has been

associated to increased levels of oxidative stress.^[27]

Because the antioxidant scavenging mechanism in the liver has been depleted, the cell has been exposed to an increased inflammatory stress, foremost to elevated level of lipid peroxidation. An antioxidative properties of organism's comprehensive antioxidant system play a very important task in time span of oxidative damage.^[8] Due to its interactions with enzymes, fluoride is a particular enzyme inhibitor because of its adhesion to the catalyst surface on the enzymes.^[28]

Oxidative mechanisms such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) have been demonstrated to be inhibited by fluoride.^[29] Fluoride can also affect glutathione levels, which can result in higher in ROS generation at the mitochondrial layer, compromising molecular function. GSH functions as a primary scavenging of radicals, a co-substrate for a variety of enzymes, and a source of adducts in endo and xenobiotic activities.^{[30],[31]}

In mice bearing fluoride-treated soft tissues, lipid peroxidation increased and enzymatic antioxidants activity decreased. The decrease in GSH levels seen in rats treated with fluoride shows increased consumption as a result of oxidative stress. Reduced GPx activity may result in negative oxidative modifications as a result of the accumulation of hazardous compounds. GPx utilises GSH to metabolise H₂O₂ (hydrogen peroxide) to (water) H₂O. (hydrogen donor).^[32] When ROS levels are elevated, the cellular antioxidant defence mechanism is affected. Fluoride has an influence on GSH's antioxidant potential as well as a number of enzymes which use GSH as a coenzyme.^[31]

Fluoride exposure was reported to decrease GSH levels. The ratio of GSH/GSSG is one of the assess of oxidative stress.^[33] As per various studies were determined that fluoride produces oxidative stress at relatively low doses while functioning as an activator of free radical production at higher quantities.^[34] SOD concentrations were shown to be decreased in mice soft tissues showing to high concentration of fluoride. SOD and, CAT activities were discovered to be decreased in the experimental animal's organs like liver, kidney. SOD is one of the antioxidant enzymes which degrade superoxide •O₂ to H₂O₂.^[35] CAT is heme protein, degrades H₂O₂ and protects tissues from the damaging effects of (OH•) hydroxyl radicals.^[36] The decreased activity of these enzymes causes oxidative stress generated by fluoride poisoning.

Superoxide dismutase (SOD) is a key antioxidant enzyme in the body that works in concert with glutathione to convert superoxide to harmless hydrogen peroxide and water, thereby protecting the organism against superoxide toxicity. This shields cells from the harm caused by active oxygen to DNA and other biological

macromolecules. Fluoride has been demonstrated to inhibit SOD and GSH activity in tissue, which may result in the gathering of ROS. Fluoride disclosure may result in the creation of superoxide anion O₂⁻ (MDA). Fluoride exposure has previously been shown to increase lipid peroxidation levels in animals and humans. Fluoride exposure has previously been shown to increase lipid peroxidation levels in animals and humans.^{[22], [30], [37]}

Fluoride exposure mediated excitotoxicity mechanism

Fluoride's excitotoxicity has been linked to microglial activation, which may play a role in fluoride's neurotoxicity. A connection between the system and many neurological disorders, as well as neurotoxin effects and heavy metal toxicity, has been established. When glutamate receptors in neurons are overloaded, excitotoxicity occurs, causing the microglia to release cytokines and other immune factors. As a result, the immune system is triggered, resulting in brain cell death. The glutamate transporters in the brain have been blocked, which is thought to be the cause of the excess glutamate being stored. Oxidative stress, aldehyde and nitrosative stress, and ROS and RNS all play a role in ecotoxicity.^[38]

Fluoride neurodegeneration is predominantly caused by excitotoxicity, and arguments in favour of this hypothesis are presented, along with some secondary data in support of the notion (excitotoxicity in fluorosis). When fluoride accumulates in the dentate gyrus, hippocampus, as well as other parts of the cortex and amygdala, it damages the brain's neurons, according to studies done on animals. Fluoride is probably the first inorganic ion to receive research attention for its negative effects, and fluoride poisoning from drinking water is now well recognised as a worldwide issue. Excessive excitotoxicity is a major contributor to fluoride-induced neurodevelopmental diseases.^{[41],[42]} The molecular framework of neuroinflammation begins at the molecular level, where primary causes, oxidative stress and excitotoxicity, act continually to inflict the large proportion of cell injury and destruction.

Death of cells in the brain is caused by fluoride

For persistent fluoride exposure, abnormal cell architecture is formed in the brain. Animal species bare to immense level of fluoride ion, either frankly or ultimately through the mother, have been found to have abnormalities in their brain tissue during the foetal and weaning periods. ^{[43], [44]}. After passing via the placenta of women with chronic fluorosis, fluoride deposition in the hippocampus of the foetus has been shown to have a deleterious impact on brain maturation. According to various studies, fetuses born in regions with widespread exposure to fluoride throughout the 5th to 8th months of pregnancy had a much smaller brain than those born in regions with no exposure.^[42] Foetuses from fluorosis-prone areas had lower volumes of neurons, volume density, and mitochondrial surface densities than those from non-fluorosis-prone

areas.^[43] 45 ppm of fluoride and, 90 days iodine deficiency resulted in neuronal toxic changes occur in the brains of young animals.^[45]^[46].

Fluoride-induced animals have had their brain morphology examined for a range of alterations. During their embryonic, weaning, and post-weaning (maternal) periods of life, rats were fed moreover 30 otherwise 100 parts per million fluoride (as NaF) in intake water. There was no visible abnormality in brain histology of young animals bare to 30 parts per million of fluoride compared to animals uncovered to 100 ppm, which resulted in considerable degenerative abnormalities in areas of the brain. When sodium fluoride (5-50 mg/mL/kg per day for 15 weeks) was injected subcutaneously into rabbits' brains, the number of Purkinje cells in the cerebellum decreased significantly, as did evidence of chromatolysis and gliosis in the motor cortex.^[45]^[46].

Fluoride metabolism in brain

Fluoride inhibits several enzymes that require divalent cations as coenzymes. In addition, fluoride is harmful to people's health. Fluoride-resistant enzymes include those involved in energy metabolism, protein and amino acid metabolism, and free radical scavenging. Consequently, because of its ability to alter cellular processes in human tissues, fluoride is classified as a metabolic toxin.^[47]^[48]^[49] Furthermore, studies have indicated that fluoride water (as NaF) inhibits enzyme activity, lipid, amino acid, and nucleic acid metabolism, and brain cell communication.^[50]^[51].

Brain membrane triglyceride levels were altered by fluoride treatment (30 or 100 ppm for 3 to 7 months).^[52] Neuronal cell membrane phosphatidyl serine, phosphatidyl choline and phosphatidyl ethanolamine levels were lowered by sodium fluoride injection, but ubiquinone levels were increased.^[53] Fluoride injections of (5-50 mg/kg/d) for 100 days are said to have enhanced lipids in rabbit brains. Over the course of 14 days, fluoride poisoning reduced the activity of enzymes involved in energy metabolism, alanine aminotransferase, lactate dehydrogenase, AST, SDH, and CK activity in mice, which is dependable with the result of earlier studies.^[25].

Fluoride interferes with the function of enzymes that maintain the integrity of the membrane and the transmission of nerve impulses. Fluoride inhibited the activity of calcium ATPase, sodium-potassium ATPase, magnesium ATPase and, acetyl cholinesterase in the brain.^[25] Neuronal cell acetylcholinesterase (AChE) and butyryl cholinesterase (BChE) activities were lowered in rats fed fluoride concentrations of 5 or 50 percent over six months.^[53] However, prenatal exposure to high fluoride levels (5, 15, and 50 ppm Fluoride) resulted in enhanced acetylcholinesterase activity in cerebral axonal membranes, and sustained treatment after delivery for 80 days contributed to this effect. In the brains of sodium fluoride (NaF)-induced rats, researchers reported a considerable decrease in the

amount of nicotinic acetylcholine receptors.^[53]

Only a handful of authors have documented the harmful effects of fluoride in brain's nucleic acids, protein and, amino acids. RNA (ribo nucleic acid), DNA (deoxy ribo nucleic acid), and protein concentration in cerebral hemisphere and, cerebellum was extensively reduced in mice after 30 days of oral therapy with 6 and, 12 mg/kg body weight/day of NaF. After stopping the therapy for 30 days, there was some improvement, although it was not complete. Fluoride poisoning in rabbits was associated with increases in free amino acids in the hippocampus.^[54]

CONCLUSION

Ten of the 29 districts in the state of Tamil Nadu (India) had fluoride levels that were significantly above the national average. According to data from the Tamil Nadu Department of Water Resources (TDWR), the fluoride levels in the state's groundwater are highest in the districts of Dharmapuri (the state's capital), Krishnagiri (the state's second-highest), and Salem. Fluoride is toxic to the nervous system, causing free radicals, oxidative stress, cognitive impairment, behavioural changes, and ultimately the death of neuronal cells. Fluoride is found in many common household products. Fluoride-induced brain injuries can be better understood with the help of this review.

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How to cite this article

Sathasivam Rajkumar, Swaminathan Gomathi, Chinnadurai Kannan, Byran Gowramma, Ramanathan Sambathkumar, 2021. Fluoride, Oxidative Stress, Ground water, Neurotoxicity, Anti-oxidants. *Jour. of Med. P'ceutical & Allied. Sci.* V 10 - I 6, 1698, P- 3910 - 3915. doi: 10.22270/jmpas.V10I6.1698