FLUORIDE AND IMPACT OF OCCUPATION EXPOSURE

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Abstract:

Fluoride, a naturally occurring element, finds widespread applications in various industries, contributing to improved dental health, metallurgy, glassmaking, and pesticide production. Despite its positive effects, fluoride's occupational impact has raised concerns due to potential health risks associated with prolonged or excessive exposure.

The dental industry relies heavily on fluoride to prevent tooth decay and cavities. However, professionals working with fluoride-based products may encounter skin and eye irritation, highlighting the importance of adopting appropriate safety measures. Additionally, community water fluoridation has been linked to enhanced dental health but requires meticulous monitoring to prevent excessive exposure.

In metallurgical and glass industries, fluoride compounds are utilized in metal production and glass manufacturing processes. Workers in these sectors face risks of fluoride inhalation, leading to respiratory issues and skeletal fluorosis. Occupational health measures such as proper ventilation and personal protective equipment are imperative to safeguard employee well-being.

Furthermore, certain fluoride-containing compounds are used as pesticides, necessitating precautions for workers handling these chemicals. Monitoring and adherence to established safety guidelines can minimize the risk of exposure-related health issues.

Regulatory bodies have set permissible exposure limits (PELs) for fluoride to protect workers. Compliance with these guidelines and the implementation of comprehensive occupational hygiene and safety practices are paramount in mitigating the impact of fluoride exposure.

The discussion of relevant case studies further illustrates the real-world impact of fluoride exposure in different occupational settings. By fostering a culture of safety and implementing preventive measures, industries can ensure the well-being of their workforce and mitigate potential health risks associated with fluoride exposure in occupational settings.

Keywords: Permissible exposure limits (PELs), Occupational impact, fluorosis, Regulatory compliance

Introduction

Fluoride, the anion of fluorine, is a naturally occurring substance found in both soil and water. Fluorine is a highly abundant element, ranking as the 13th most plentiful element in Earth's crust. The reduced form of fluorine is known as fluoride whether present as bound to other elements or as an ion.

Physicochemical properties:

Fluoride is a chemical compound that has several physicochemical properties. Fluorine is small and has van der Waals radius 1.47 Å [Shah P et. al 2007]. Fluorine is one of the most electronegative elements and is the most reactive non-metal [Fluoride Ion | F- - PubChem (nih.gov)]. Therefore, it combines with another element (except nitrogen, noble gases, and oxygen) and forms a compound, fluoride. It is a highly reactive anion, which means it readily forms compounds with almost all other elements except neon and helium [Martínez-Mier EA 2012]. The low stability of the F-F bond (which is thermodynamically unstable) results in high reactivity, as it lowers the activation energy required for reactions (making it kinetically unstable) [Pomeroy RK 2015].

Fluoride has a low boiling point and melting point, and it is highly soluble in water. It attracts electrons toward itself due to high electronegativity [Fluoride Ion | F- - PubChem (nih.gov)]. This property makes fluoride a powerful oxidizing agent that can react with other compounds to release energy[Fluoride Ion | F- - PubChem (nih.gov)]. In addition, fluoride can form complexes with metal ions, which has important implications for its use in industrial processes and water treatment. When exploring the impact of fluorine on medicinal chemistry, it becomes apparent that the addition of a single fluorine atom or trifluoromethyl group in a crucial position of a biologically active molecule can have a significant impact on its pharmacological properties [Shah P et. al 2007]. Overall, the physicochemical properties of fluoride make it a unique and versatile compound with a wide range of applications in various fields.

Table1: A brief overview of fluorine and fluoride as a compound [Nuclear Power 2021; Pubchem]

Properties	Values for Fluorine	Values for Fluoride (Sodium fluoride)
Atomic number	9	
Atomic mass	18.9984 u	41.988173 g/mol
oxidation states	-1	0
Density	1.696 g/cm^3	2.558 g/cm^3
Electron Affinity	-328 kJ/mol	
Electronegativity	3.98	3.05
Melting point	**-219.8°C**	**1,000°C**
Boiling point	**-188.1°C**	1,700°C
Solubility [at 25 °C]	0.00169 mg/mL	42,900 mg/L

Types of fluoride molecules available**:** Fluoride molecules can refer to different types of molecules containing the fluoride ion (F-). For example, sodium fluoride (NaF) contains one fluoride ion per molecule, while calcium fluoride (CaF2) contains two fluoride ions per molecule. There are 39 molecules available till date. (Refer to table). Inorganic fluoride compounds such as sodium fluoride, hydrogen fluoride, and calcium fluoride are often used in industries and can pose health risks to workers if not handled properly. On the other hand, fluoride ions are also present in many natural minerals and in small amounts in drinking water and toothpaste, and have been shown to have benefits for dental health. [CDC 2022]

Table 2: Depicting key properties of Fluoride compound [Schneider, 2023; Dehnen S 2021].

S.No.	Properties	Description	Examples
1	Ionic or covalent bonds	Fluoride can form either ionic bonds (when it transfers an electron to a metal) or covalent bonds (when it shares an electron with a nonmetal)	1. ionic compound- sodium fluoride (NaF) 2. covalent compound - carbon tetrafluoride (CF4)
2	High electronegativity	Fluorine is the most electronegative element, meaning it has a strong tendency to attract electrons. This makes fluoride molecules very polar (having unequal charge distribution) and reactive	fluorine can react with almost all other elements except helium and neon
3	Basicity	Fluoride is a weak base, meaning it can accept a proton (H+) from an acid.	fluoride can react with water to form hydrofluoric acid (HF) and hydroxide ion (OH−): F− + H2O → HF + OH−
4	Structure	Fluoride molecules can have different shapes depending on the number and arrangement of atoms	1. fluorine gas (F2) has a **linear** shape, 2. sulfur hexafluoride (SF6) has an **octahedral** shape 3. xenon difluoride (XeF2) has a **bent** shape

5.	Biochemistry	Fluoride can interact with biological molecules and enzymes, sometimes affecting their function.	fluoride can inhibit the activity of some glycolytic enzymes, which are involved in breaking down glucose for energy

Industry Usage of Fluoride:

Fluoride is widely used in various industries for its unique properties and applications. One of the primary uses of fluoride is in the production of aluminum. Fluoride is added during the aluminum smelting process to lower the melting point of the aluminum oxide, allowing for more efficient production. [Kvande H, 2014]

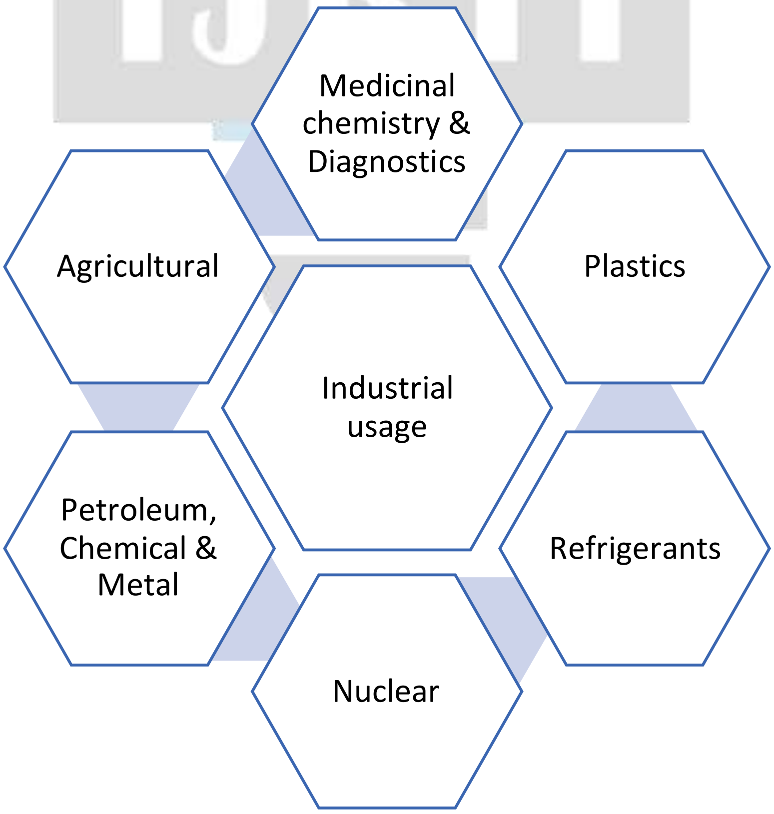
In the chemical industry, fluoride compounds are utilized as catalysts in various reactions. [Li M et al, 2021] They play a crucial role in organic synthesis, petroleum refining, and the production of certain plastics and polymers. Fluoride compounds are also used in the manufacture of pharmaceuticals, agrochemicals, and fluoropolymers. [Znidar D et. al, 2022]

Fluoride's ability to strengthen and protect materials from corrosion has led to its use in the production of glass, ceramics, and enamels. It is also employed in the production of electronic components and as a flux in soldering applications. [Li X 2021]

Additionally, fluoride compounds find application in water treatment processes. Sodium fluoride is commonly added to public water supplies as a means of preventing tooth decay and promoting dental health.

While fluoride has numerous industrial uses, it is essential to handle and dispose of fluoride compounds responsibly to minimize potential environmental impacts. Strict regulations and control measures are in place to ensure the safe and sustainable utilization of fluoride in industry.

Figure 1: Industrial exploitation of fluoride [Shah P et. al 2007; Choudhary S 2019; Wilson JN, 1973; Mullenix PJ, 2014; Thomas M 1930; Choubisa SL, 2016; Crouse PL , 2015]



1. Hydrofluoric acid (HF): It is used in the petroleum, chemical, and metal industries as a catalyst and solvent, as well as in the production of refrigerants, plastics [U.S. EPA 2018], and pharmaceuticals. [Abdollahi M, 2014]

2. Sodium fluoride (NaF): It is used in the production of insecticides, fungicides, and rodenticides, as well as in water fluoridation to prevent tooth decay. [Jha SK 2011]

3. Fluorinated polymers, such as polytetrafluoroethylene (PTFE) and polyvinylidene fluoride (PVDF), are used to produce non-stick coatings, waterproof membranes, and electrical insulation. [Cardoso VF, 2018]

4. Fluorine gas (F2): It is used in the production of uranium hexafluoride, which is used in the nuclear industry for uranium enrichment. [Hexafluoride U, 1991]

5. Sodium monofluorophosphate (Na2PO3F): It is used in toothpaste as an anti-cavity agent. [Saporito RA, 2000]

Guidelines reference

In the context of fluoride occupations, guidelines are important for ensuring that workers are protected from potential health hazards associated with exposure to fluoride.

Guidelines play a crucial role in regulating occupational exposure to fluoride. They help to establish safe levels of exposure and provide recommendations on appropriate protective measures to prevent or minimize potential health risks. These guidelines are typically established by regulatory agencies or professional organizations that specialize in occupational health and safety

For example, the Occupational Safety and Health Administration (OSHA) in the United States has established a permissible exposure limit (PEL) of 2.5 mg/m^3 for airborne fluoride in the workplace. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) of 1.5 mg/m^3 for airborne fluoride.

Here are some guidelines and references for fluoride usage and toxicity:

The World Health Organization [WHO, 2006] recommends a fluoride concentration of 0.5 to 1.5 mg/L in drinking water for optimal dental health, with a maximum guideline value of 1.5 mg/L to prevent dental fluorosis.

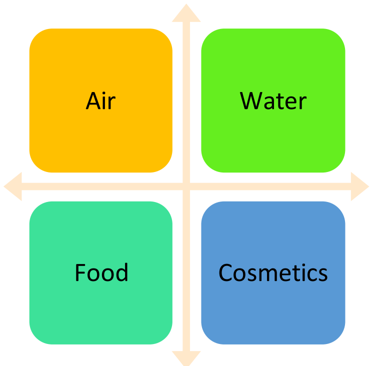
The American Dental Association (ADA) recommends that children under 3 years old use a smear of toothpaste containing no more than 1000 ppm fluoride, while children aged 3-6 use a pea-sized amount of toothpaste containing no more than 1000 ppm fluoride [ADA, 2019].

The Environmental Protection Agency (EPA) has established a maximum contaminant level (MCL) of 4.0 mg/L for fluoride in public water systems, to prevent adverse health effects [EPA, 2022].

The Agency for Toxic Substances and Disease Registry (ATSDR) has established a minimal risk level (MRL) of 0.05 mg/kg/day for chronic oral exposure to fluoride, to prevent adverse health effects [ATSDR, 2003].

It's important to note that the recommended limits and guidelines for fluoride intake may vary depending on the individual's age, weight, and overall health. Adherence to these guidelines is important for ensuring the health and safety of workers in fluoride occupations. Employers are responsible for ensuring that their workers are aware of the guidelines and that appropriate measures are in place to minimize exposure to fluoride. Workers, in turn, should be trained on the proper use of protective equipment and techniques for minimizing their exposure to fluoride in the workplace.

Figure 2: four possible ways of contamination



Ways of taking fluoride (dermal, inhalation, oral uptake) [Pubchem]

Routes of administration of fluoride

As a naturally occurring element, fluoride is readily available to humans both intentionally and unintentionally. Exposure to fluoride can occur through various resources. We are considering three ways of exposure

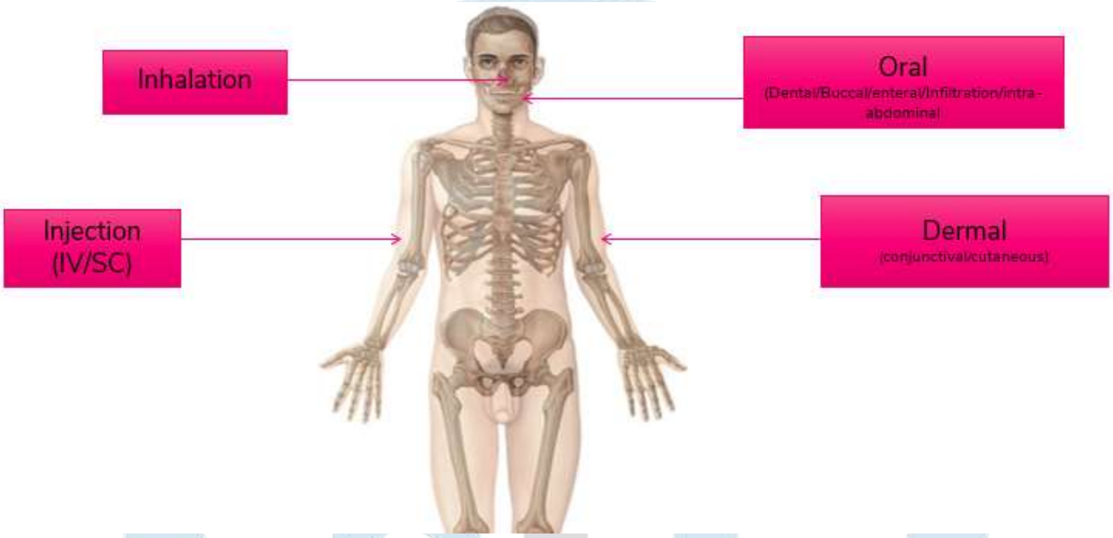


Figure: Route of exposure of fluoride [Pubchem]

Oral [Whitford GM, 1996]

Fluoride is a common substance that is often ingested orally through water, food, and supplements. Both inorganic and organic are ubiquitous and therefore fluoride gets into the system. The oral absorption of fluoride is influenced by several factors, including the concentration and form of the fluoride, as well as the physiological conditions of the gastrointestinal tract.

The fluoridation method could be added to natural sources like water, milk, and salt) or as a dietary supplement like tablets or drops, Chewable tablets, lorezen) [Abdollahi M, 2014]. Water fluoridation includes hydrofluorosilicate (FSA), sodium fluorosilicate, and sodium fluoride in the concentration of 0.7-1.2 mg/l and milk fluoridation includes sodium fluoride or disodium Mono fluorophosphate in the concentration of 5mg/l is recommended. Approx. 250-300 mg/kg is the recommended concentration for salt fluoridation [Cerklewski FL, 1997; Aoun A, 2018].

Fluoride is absorbed primarily in the small intestine by passive diffusion, which is influenced by the pH of the intestinal fluid. [Buzalaf, MAR 2011; Zohoori, FV 2017; Whitford, GM 1996] When the pH is acidic, fluoride exists in a more ionized form, which reduces its absorption [Martínez-Mier EA 2012; Whitford, GM 1996]. In contrast, when the pH is alkaline, the fluoride is in a less ionized form, which facilitates its absorption [Whitford, GM 1996].

The bioavailability of fluoride depends on the chemical form in which it is ingested. Fluoride salts, such as sodium fluoride and sodium monofluorophosphate, are readily absorbed in the stomach and small intestine [Cerklewski, FL 1997]. In contrast, the bioavailability of fluoride from natural sources, such as fluoridated water and tea, is relatively low because fluoride is present in an insoluble form and must be released through the action of acid in the stomach [Jha SK, 2011].

Additionally, the presence of other substances in the GI tract can affect the absorption of fluoride. For example, the presence of calcium can reduce the absorption of fluoride by forming insoluble calcium-fluoride complexes [ATSDR, 2003].

After being absorbed, a certain amount of fluoride gets stored in the bones, while the rest is eliminated from the body through urine, feces, sweat, and saliva. [Fluoride Ion | F- - PubChem (nih.gov)]

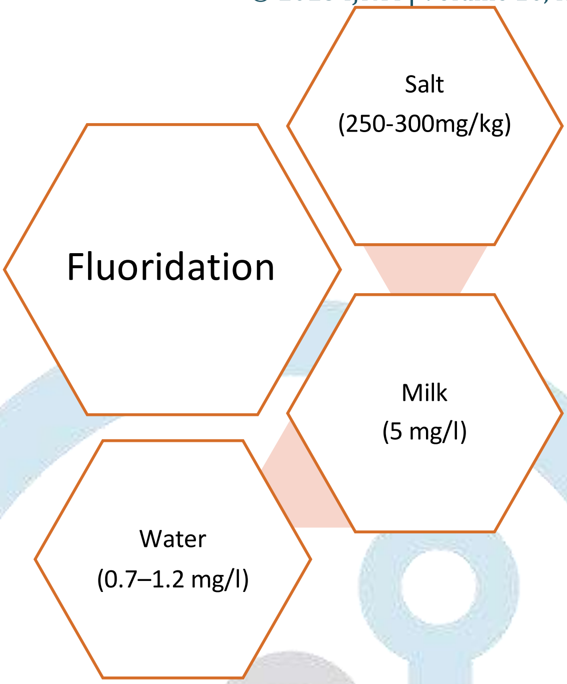


Figure 3: depicting permissible limit of fluoridation [Aoun A, 2018; Sampaio FC,2011.]

Dermal

Fluoride **dermal absorption** refers to the process by which fluoride can be absorbed through the skin and enter the body. While dermal absorption of fluoride is generally considered to be a less significant route of exposure compared to ingestion, it can still contribute to overall fluoride exposure in certain situations. Due to its ionic nature, fluoride is anticipated to have low membrane permeability [ATSDR, 2003].

For example, individuals who work with fluoride-containing products or live near industrial sources of fluoride emissions may be at increased risk of dermal exposure. Additionally, certain skin conditions or injuries may increase the permeability of the skin, making it more susceptible to fluoride absorption. However, the extent of fluoride dermal absorption and its potential health effects are still the subject of ongoing research and debate [ATSDR, 2003].

Inhalation

Inhalation is another route of exposure to fluoride, particularly in occupational settings where workers may inhale fluoride-containing dust or fumes. This can occur in industries such as aluminum production, phosphate fertilizer production, and welding. Chronic inhalation exposure to high levels of fluoride can cause respiratory symptoms. Fluoride can be emitted into the air in several different formats, depending on the specific source of the emission [ATSDR, 2003].

- **Gaseous fluoride compounds**: Fluoride can be released into the air as gaseous compounds, such as hydrogen fluoride (HF) or nitrogen trifluoride (NF3), which can be produced during industrial processes or as a by-product of certain chemical reactions [CDC, 2022].
- **Particulate fluoride compounds**: Fluoride can also be released into the air as particulate compounds, such as sodium fluoride (NaF) or calcium fluoride (CaF2), which can be generated through activities such as mining or the use of certain fertilizers [CDC, 2022].
- **Fluorinated greenhouse gases**: As mentioned in a previous response, fluorinated greenhouse gases (GHGs) like hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), and sulfur hexafluoride (SF6) can also be emitted into the air, and contribute to the greenhouse effect and global warming [CDC, 2022].

Overall, the specific format in which fluoride is emitted into the air can vary depending on the specific source of the emission and can have different implications for human health and the environment.

The use of hydrogen fluoride/hydrofluoric acid in various industries, such as semiconductor manufacturing, chemical production, and laundry, can contribute to the release of fluoride into the environment. Fluoride is also present in various industrial products, such as insecticides, rodenticides, floor polishes, and timber preservation, which can further contaminate the environment [Ahmad S, 2022].

Additionally, some areas with high levels of naturally occurring fluoride in rocks can be heavily affected by industrial activities, leading to increased fluoride levels in water and food sources [Ahmad S, 2022]. Furthermore, excess fluoride in the environment can lead to health issues for both humans and animals, such as endemic fluorosis. Therefore, it is crucial to implement effective measures to control and minimize fluoride pollution from industrial activities to protect the environment and public health.

Fluorinated greenhouse gases (GHGs) are a group of human-made compounds that contain fluorine and contribute to global warming by trapping heat in the atmosphere. These gases include hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), sulfur hexafluoride (SF6), nitrogen trifluoride (NF3), and other fully fluorinated GHGs [U.S. EPA 2018]. While these gases make up a small percentage of total greenhouse gas emissions, they are particularly potent in their ability to trap heat in the atmosphere and contribute to climate change [U.S. EPA 2018]. As such, reducing emissions of fluorinated GHGs has become an important focus of global efforts to mitigate climate change. These GHGs can be released into the atmosphere during F-gas production as by-products, reactants, intermediates, or final products [European Environment Agency, 2021].

Apart from industrial activities, volcanic eruptions also significantly impact the environment, leading to higher concentrations of fluoride in the air in affected areas. Volcanic eruptions can release significant amounts of fluorine gas into the atmosphere, leading to increased concentrations of fluoride in the air in affected areas. These emissions can come from various volcanic activities, including explosive eruptions, lava flows, and fumaroles. [Fuge R, 2019]

When fluoride is released into the atmosphere, it can react with water vapor, forming hydrogen fluoride and other fluoride compounds, which can be transported over long distances and deposited on the ground. This can result in the contamination of soil and water, leading to increased exposure of humans and animals to fluoride [US EPA, 2022]

Exposure of plants to fluoride can occur through several different pathways, including uptake from soil, air, or water. Depending on the concentration and duration of exposure, fluoride can have both positive and negative effects on plant growth and development. For example, low to moderate concentrations of fluoride can stimulate plant growth and improve resistance to certain types of stress, such as salt or heavy metal toxicity [Sharma, R, 2018]. However, fluoride can be toxic to plants at higher concentrations, causing symptoms such as leaf necrosis, reduced root growth, and decreased chlorophyll content [Meharg, AA, 2003]. The specific effects of fluoride on plant growth can vary depending on factors such as plant species, age, and environmental conditions.

Fluoride accumulates on the external layer of leaves in plants. When animals or humans consume these plants, fluoride enters their system. Fluoride is absorbed from the gastrointestinal tract and distributed to the bones and teeth, where it accumulates over time. The metabolism of fluoride is limited, and it is mainly excreted through the kidneys. However, some fluoride can also be excreted through sweat and feces.

Injection: Fluoride injection is a medical procedure where a solution of fluoride is injected into the bloodstream. This is typically done as a treatment for osteoporosis, a condition characterized by weakened bones that are more prone to fractures. Fluoride injections have been shown to increase bone density and reduce the risk of fractures in people with osteoporosis [Cosman, F, 2014; Bohatyrewicz A, 1998; Watts NB, 2010; Black DM 1996].

Metabolism of fluoride

The metabolism of fluoride-containing compounds varies greatly due to their diverse nature. Its uptake in the body involves a complex process that depends on various factors such as the source of fluoride, the form in which it is ingested, and the individual's age and overall health status [U.S. Environmental Protection Agency, 2010]. Once inside the body, fluoride can undergo biochemical modifications, which can result in the formation of different fluoride-containing compounds. Factors such as reactivity, structure, solubility, and fluoride ion release ability play a significant role [Martínez-Mier EA 2012]. When fluoride is ingested, it is rapidly absorbed into the bloodstream and distributed throughout the body, including the bones and teeth [Centers for Disease Control and Prevention, 2021]. Fluoride ions are then excreted from the body via the kidneys and urine [Malin AJ, 2019]. In addition to ingestion, fluoride can also be absorbed through inhalation or dermal contact with fluoride-containing products or substances [Centers for Disease Control and Prevention, 2021]. These compounds can be metabolized differently, depending on their reactivity and structure, solubility, and ability to release fluoride ions [Martínez-Mier EA 2012]. The ionic form of fluoride that is generated within the body or ingested directly can be metabolized in a relatively simple manner. Fluoride ions can combine with calcium and phosphate ions in the body to form fluorapatite, which is then deposited in the bones and teeth, where it can contribute to their strength and durability [Centers for Disease Control and Prevention, 2021].

However, excessive fluoride intake can lead to dental and skeletal fluorosis, which is characterized by changes in the structure and strength of the teeth and bones. To prevent these conditions, it's important to maintain a balance between the intake and excretion of fluoride in the body [Martínez-Mier EA 2012].

After being absorbed, fluoride quickly spreads throughout the body via the bloodstream, with a plasma half-life ranging from 3 to 10 hours [Whitford GM, 1996]. Plasma fluoride levels are directly related to the amount of fluoride intake, and they are not regulated homeostatically. Furthermore, fluoride is distributed between the plasma and blood cells, with plasma levels being higher than blood cell levels. Additionally, the saliva fluoride level is about 65% of the level in plasma [Ekstrand 1977].

Renal excretion is the primary means of fluoride removal from the body. The fluoride ion is filtered from the plasma by the glomerulus and then partially reabsorbed; there is no tubular secretion of fluoride [Whitford GM. 1996, CDC, 2022]. The rate of fluoride clearance is influenced by a number of factors, including the rates of bone accretion and dissolution, urinary pH, urinary flow, and glomerular filtration rate [Whitford GM. 1996, CDC, 2022]. While there are no apparent age-related differences in renal clearance rates between children and adults, there is a significant decline in renal clearance of fluoride in older adults, consistent with the age-related decline in glomerular filtration rates [Whitford GM. 1996, CDC, 2022].

Almost 99% of the fluoride in the human body is found in bones and teeth, where it replaces the hydroxyl ion in hydroxyapatite to form fluorohydroxyapatite [Clarkson JJ, 2000; ATSDR, 2003]. The level of fluoride in bone is affected by various factors, such as age, past and present fluoride intake, and the rate of bone turnover [American Medical Association, 2021]. Fluoride can be mobilized from bone through bone remodeling [Rao HV, 1995].

Fluoride does not accumulate in soft tissues, but a higher concentration has been reported in the kidneys due to partial reabsorption. The blood-brain barrier restricts the diffusion of fluoride into the central nervous system, where the fluoride level is only about 20% of plasma. [Żwierełło W, 2023, EC,2010]. Fluoride can be transferred across the placenta, and there is a direct relationship between fluoride levels in maternal and cord blood [EC,2010]. However, fluoride is poorly transferred from plasma to milk, with the fluoride concentration in human milk ranging from 3.8–7.6 μg/L. [EC,2010]

Fluoride toxicity

Fluorine toxicity refers to the harmful effects that can be caused by excessive exposure to the chemical element fluorine or its compounds [Abdollahi M, 2014]. Fluorine is a highly reactive, non-metallic element that is widely distributed in nature and is used in a variety of industrial and consumer applications, such as in the manufacture of aluminium, fluorocarbons, and dental products like toothpaste and mouthwash. [Margolis HC, 1990; Ahmad S, 2022; Lemal DM, 2004]

While small amounts of fluorine are essential for maintaining healthy teeth and bones, exposure to excessive amounts can harm human health.

Fluorine toxicity is a particular concern in areas where water or air is contaminated with high levels of fluorine, such as in some parts of India, China, and Africa [Podgorski J, 2022]. In these regions, people may be exposed to levels of fluorine that far exceed the safety limits recommended by the World Health Organization [WHO 2004].

To prevent fluorine toxicity, it is important to limit exposure to sources of fluorine, such as industrial emissions and contaminated water sources, and to use dental products containing fluorine in moderation. Water fluoridation programs are also used in some countries to provide safe and effective levels of fluorine for dental health.

The effects can be further categorized as either acute or chronic toxicity, with the route of administration or exposure playing a crucial role. Additionally, they can be classified into subcategories of topical and systemic toxicity. Excessive exposure to fluoride can cause both acute and chronic toxicity [Ullah R, 2017]. The severity of fluoride toxicity depends on the dose and duration of exposure. [Ullah R, 2017]

Acute fluoride toxicity can occur if a large amount of fluoride is ingested or inhaled at once. The symptoms of acute fluoride toxicity can include stomach pain, nausea, vomiting, diarrhea, headache, dizziness, and seizures. In severe cases, acute fluoride toxicity can lead to respiratory failure, cardiac arrest, and death. [Ullah R, 2017; Abdollahi M, 2014; Ahmad S, 2022]

Chronic fluoride toxicity, on the other hand, occurs when a person is exposed to high levels of fluoride over an extended period of time. Chronic fluoride toxicity can lead to a range of health problems, including dental fluorosis, skeletal fluorosis, and neurological symptoms such as tremors, convulsions, and muscle weakness. Dental fluorosis is characterized by mottling and discoloration of teeth, while skeletal fluorosis is characterized by joint pain, stiffness, and decreased bone density. [Ullah R, 2017; Abdollahi M, 2014; Ahmad S, 2022]

To prevent acute and chronic fluoride toxicity, it is important to limit exposure to sources of fluoride, such as industrial emissions and contaminated water sources, and to use dental products containing fluoride in moderation. Water fluoridation programs are also used in some countries to provide safe and effective levels of fluoride for dental health while avoiding excessive exposure.

Fluoride can cause both topical and systemic toxicity, depending on the route of exposure and the dose [ADA, 2021; AAPD, 2014].

Topical toxicity refers to the harmful effects of fluoride that occur at the site of contact with the body, such as the skin or mucous membranes. For example, applying high concentrations of fluoride-containing topical products like toothpaste or mouthwash directly to the gums or lips can cause irritation, ulcers, or burns. [Margolis HC, 1990]

Systemic toxicity refers to the harmful effects of fluoride that occur when it is absorbed into the bloodstream and distributed throughout the body. The most common sources of systemic fluoride exposure are through ingestion of fluoride-containing foods and beverages or through inhalation of fluoride-containing air pollutants. [Margolis HC, 1990]

Excessive systemic exposure to fluoride can cause a range of health problems, including dental fluorosis, skeletal fluorosis, and neurological symptoms such as tremors, convulsions, and muscle weakness. [Ullah R, 2017]

To prevent topical and systemic fluoride toxicity, it is important to use fluoride-containing products in moderation and to limit exposure to sources of fluoride. Water fluoridation programs are also used in some countries to provide safe and effective levels of fluoride for dental health while avoiding excessive exposure.

Enzyme level effect:[Basha PM, 2011]

Fluorine or fluoride can cause enzymatic toxicity by inhibiting various enzymes in the body. Fluoride ions have a high affinity for certain metal ions that are essential for enzyme function, such as magnesium, calcium, and iron [Ciosek Ż, 2021]. When fluoride ions bind to these metal ions, they can disrupt the structure and function of enzymes, leading to a range of toxic effects [Ciosek Ż, 2021].

Fluoride can cause enzymatic toxicity by inhibiting various enzymes in the body. Fluoride ions have a high affinity for certain metal ions that are essential for enzyme function, such as iron, magnesium, and calcium [Strunecka A, 2020; Murphy AJ 1992]. When fluoride ions bind to these metal ions, they can interrupt the structure and functionality of enzymes, leading to a range of toxic effects [Strunecka A, 2020]. Studies have found that fluoride can inhibit enzymes such as enolase, ATPases, and acetylcholinesterase, leading to effects such as muscle weakness, neurological symptoms, and metabolic disorders [Strunecka A, 2020].

One example of an enzyme that can be inhibited by fluoride is enolase, which plays a key role in glycolysis, the process by which glucose is metabolized in the body. Fluoride can bind to the magnesium ion in the active site of enolase, preventing it from catalyzing the conversion of 2-phosphoglycerate to phosphoenolpyruvate. This can lead to a build-up of 2-phosphoglycerate and a decrease in the production of ATP, which can affect cellular metabolism and energy production [Basha PM, 2011; Shivarajashankara et al. 2002].

Other enzymes that can be inhibited by fluoride include ATPases, which are responsible for maintaining ion gradients across cell membranes, and acetylcholinesterase, which is involved in the transmission of nerve impulses. Inhibition of these enzymes can lead to a range of toxic effects, including muscle weakness, neurological symptoms, and metabolic disorders [Basha PM, 2011]

Wei M et al. (2022) found that fluoride inhibits mitochondrial respiration and ATP synthesis in rat liver cells, leading to oxidative stress and hepatic dysfunction. Fina L et al. (2014) found that fluoride can impair the respiratory chain in mitochondria, leading to increased production of reactive oxygen species (ROS) and oxidative stress.

These studies provide evidence for the enzymatic effects of fluoride and highlight the importance of limiting exposure to excessive levels of fluoride to prevent its harmful effects on human health.

Overall, enzymatic toxicity is one of the mechanisms by which fluoride can cause harm to the body and highlights the importance of limiting exposure to excessive levels of fluoride.

Gene level effect

Genotoxicity refers to the ability of a chemical substance to cause damage to genetic material, such as DNA, and potentially lead to mutations and cancer. Several studies have investigated fluoride's genotoxic effects, both *in vitro* (using cell cultures) and *in vivo* (using animal models).

There are no conclusive results on the effect of fluoride on human genes. Major work is available on animal studies only [Dhar V, 2009]. There is conflicting evidence regarding the genotoxicity of fluoride. Some studies suggest that fluoride exposure may cause DNA damage, while others have found no such effects.

There are different methods and techniques to assess genotoxicity, such as the micronucleus test, chromosome aberration test, comet assay, and gene expression analysis. Some examples of case studies of genotoxicity of fluoride are:

A study by **Podder et al. (2012)** investigated the modulation of endogenous glutathione levels by fluoride in mouse bone marrow cells. The authors found that fluoride induced chromosomal aberrations, oxidative stress, and heat shock protein expression, and that these effects were influenced by the glutathione status of the cells.

A study by **Guth et al. (2020)** critically evaluated the evidence for human developmental neurotoxicity of fluoride in epidemiological studies, animal experiments, and *in vitro* analyses. The authors concluded that there was a discrepancy between experimental and epidemiological evidence and that most of the epidemiological studies had methodological limitations and confounding factors.

A study by Johnston and Strobel (2020) reviewed the principles of fluoride toxicity and the cellular response. The authors discussed the chemical properties of fluoride, its interaction with proteins and metals, its effects on organelles and pH, and its potential mechanisms of genotoxicity, such as DNA damage, oxidative stress, cell cycle disruption, and apoptosis.

A study by Ribeiro, D.A et al. (2017) analysed the putative mechanisms of genotoxicity induced by fluoride using a systematic review approach. The authors identified mitochondrial disruption, oxidative stress, and cell cycle disturbances as indicative end-points of genetic damage induced by fluoride exposure.

One of the studies investigated the genotoxic effects of fluoride in rats. The study found that exposure to high levels of fluoride (100 mg/L) was associated with DNA damage in the liver cells of rats. The study concluded that fluoride may have genotoxic effects in vivo[Ling-Fei He, 2006].

A study by **Kleinsasser NH (2001)** examined the genotoxicity and carcinogenicity of fluoride in drinking water. The authors evaluated various *in vitro* and *in vivo* assays to assess the effects on DNA and chromosomal structure and/or function. The authors found that some assays showed positive results for fluoride-induced genotoxicity, while others showed negative or inconclusive results. The authors also noted that there was no clear evidence for a causal relationship between fluoride exposure and cancer in humans or animals.

the study by Zeiger et al. (1994) reported an increase in structural chromosomal aberrations in bone marrow cells of mice exposed to high levels of sodium fluoride [Zeiger et al. (1994)]

In one of the studies, Martin et al. 1983 investigated the genotoxic effects of fluoride in several in vitro and in vivo assays. The in vitro assays included chromosomal aberrations and sister chromatid exchanges in human lymphocytes, while in vivo assays involved the analysis of micronuclei in the bone marrow cells of mice and rats. The results showed that fluoride had genotoxic effects in all the assays. The authors suggested that the genotoxic effects of fluoride may be due to its ability to interfere with DNA repair mechanisms, leading to the accumulation of DNA damage and mutations. However, it is important to note that the doses of fluoride used in these studies were relatively high and may not be relevant to human exposure levels [Martin GR, 1983]

The studies on the genotoxic effects of fluoride exposure have produced mixed results. While some studies have reported significant genotoxic effects of chronic fluoride exposure, others have found no evidence of genotoxicity. The study by Dunipace et al. (1989) showed no significant difference in the micronucleus frequency or sperm morphology between control and fluoride-exposed groups [Dunipace et al., 1989]. The study by Li et al. (1987) also found no genotoxic effects of fluoride exposure on bone marrow cells in the mouse micronucleus test. However, Li et al. (1987, 1989) reported a significant increase in sister chromatid exchanges in lymphocytes of rats and mice exposed to chronic fluoride, suggesting that fluoride exposure may cause chromosomal damage [Li et al. (1987, 1989)].

The author investigated that animal on the high fluoride diet exhibited a significant increase in the frequencies of sister chromatid exchanges (SCEs) compared to those on the low fluoride diet. This suggests that high levels of fluoride in the diet may induce genetic alterations and increase the occurrence of SCE. [Kram D, 1978]

Overall, further research is needed to fully understand the genotoxic effects of chronic fluoride exposure

Adverse effects: [Ullah R, 2017; Abdollahi M, 2014; Ahmad S, 2022]
Fluorine and fluoride are naturally occurring elements that can be found in water, soil, and some foods. While they can have beneficial effects on dental health and bone strength when consumed in appropriate amounts, overexposure to these elements can cause adverse effects.

Fluorine is a highly reactive gas and is not typically encountered in its pure form. However, it is often used in industry to produce fluorine-containing compounds, such as hydrofluoric acid and various fluoropolymers. Exposure to fluorine gas or its compounds can be dangerous and cause severe health effects, such as respiratory and cardiac issues.

Fluoride is a form of fluorine that is commonly added to drinking water and toothpaste to prevent tooth decay. While it is generally safe when consumed in recommended doses, overexposure to fluoride can lead to dental fluorosis (which affects tooth enamel and causes discoloration and pitting) and skeletal fluorosis (which affects bone density and can cause joint pain and stiffness). In extreme cases, fluoride toxicity can cause seizures, cardiac arrhythmias, and even death.

Overall, it is important to be aware of the potential adverse effects of fluorine and fluoride and take appropriate precautions to avoid overexposure.

Fluorine exposure can cause various symptoms, including but not limited to [Whitford GM. 1996; WHO 2006]]:

- Skin irritation
- Eye irritation or damage
- Respiratory issues, such as coughing or difficulty breathing
- Gastrointestinal problems, such as nausea, vomiting, or abdominal pain
- Weakness or fatigue
- Muscle spasms or tremors
- Seizures
- Cardiac arrhythmias
- Dental fluorosis (a condition that affects tooth enamel and causes discoloration and pitting) with chronic exposure to high levels of fluoride.

Fluoride exposure can cause various symptoms, including but not limited to [WHO, 2006]:

- Dental fluorosis (a condition that affects tooth enamel and causes discoloration and pitting) with chronic exposure to high levels of fluoride. Dental fluorosis occurs when too much fluoride is ingested during tooth development, leading to discoloured or pitted teeth
- Skeletal fluorosis, which can cause joint pain, stiffness, and fractures. Skeletal fluorosis occurs when fluoride accumulates in bones over time, causing joint pain, stiffness, and decreased bone density.
- Weakness or fatigue
- Numbness or tingling in the extremities
- Gastrointestinal problems, such as nausea, vomiting, or diarrhea
- Respiratory issues, such as coughing or difficulty breathing
- Skin irritation or rash
- Eye irritation or damage
- Cardiac arrhythmias, in rare cases with high levels of exposure.

It's important to note that the severity of these symptoms can vary depending on the level and duration of fluoride exposure.

Case Studies

1. The study conducted by Yadav, Lata, Kataria, and Kumar in 2009 focused on assessing the fluoride distribution in groundwater and surveying the prevalence of dental fluorosis among school children in the villages of the Jhajjar District in Haryana, India. The researchers collected water samples from various sources such as hand pumps and tube wells and measured the fluoride levels using appropriate analytical techniques. Additionally, they conducted a survey among school children to determine the prevalence and severity of dental fluorosis. The results revealed that a significant number of water sources had fluoride concentrations above the permissible limits set by the World Health Organization (WHO). Furthermore, the survey showed a high prevalence of dental fluorosis among the children, indicating a potential health concern due to excessive fluoride exposure from groundwater sources in the studied area. This study provided valuable insights into the fluoride contamination

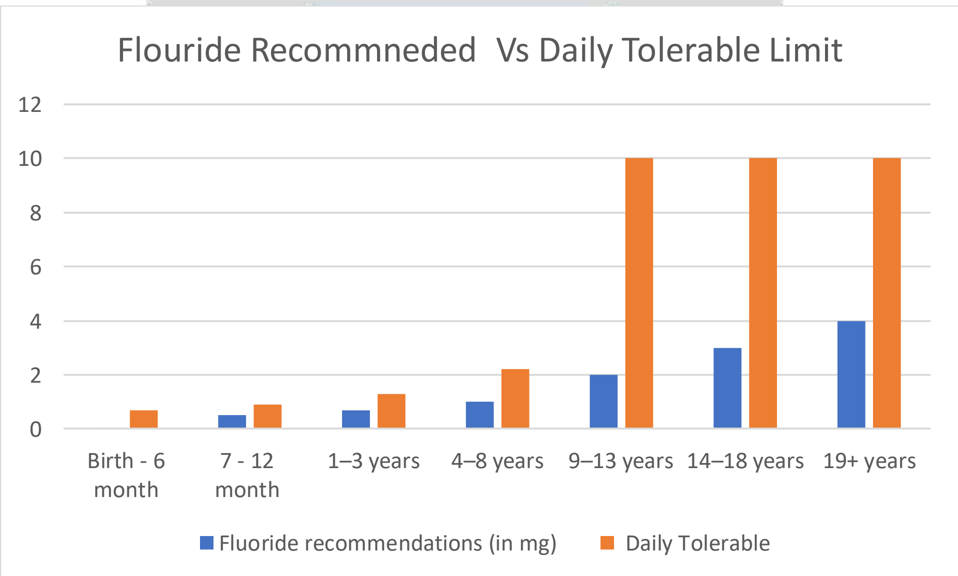
issue in the region and highlighted the need for effective mitigation strategies to ensure the provision of safe drinking water to the local population.

2. "Endemic fluorosis in an adult in the United States" by Ayoob et al. (2008): This case report describes an adult male who presented with severe skeletal fluorosis. The patient had been exposed to high levels of fluoride through drinking well water contaminated with naturally occurring fluoride. The fluoride concentration in the well water was found to be 14.2 mg/L, which is much higher than the recommended level of 0.7-1.2 mg/L set by the US Environmental Protection Agency (EPA). The patient had been drinking this water for over 20 years and had developed crippling bone pain, muscle weakness, and difficulty walking. X-rays and bone scans revealed severe skeletal fluorosis, which had caused extensive calcification of the ligaments and tendons throughout his body.
3. "Endemic fluorosis in Turkish patients: relationship with knee osteoarthritis" by Savas et al. (2001): This study investigated the association between endemic fluorosis and knee osteoarthritis in a Turkish population. The results showed a significant association between the two conditions, with a higher prevalence of knee osteoarthritis in the fluorosis group. The authors suggest that fluoride may contribute to the development of osteoarthritis by causing damage to joint cartilage and bones. The study highlights the need for further research on the long-term effects of fluoride exposure on joint health.

4. "Fluorosis in cattle in the Wairarapa region of New Zealand" by Cronin et al. (2000): This case series describes an outbreak of fluorosis in cattle in the Wairarapa region of New Zealand. The authors suggest that the fluoride contamination was due to the use of phosphate fertilizers on pastures. The cattle developed dental fluorosis, which caused discoloration and weakening of their teeth, and skeletal fluorosis, which caused lameness, stiffness, and joint pain. The authors suggest that farmers should be aware of the potential for fluoride contamination in their pastures and take measures to prevent excessive exposure.

5. "Fluoride Metabolism in Patients With Chronic Renal Failure" by Herta Spencer et al. (1980): The study aimed to understand the impact of renal dysfunction on fluoride levels and its excretion in the body. The author conducted experiments and measurements on a group of patients with chronic renal failure to assess their fluoride metabolism. The results revealed that patients with impaired renal function exhibited altered fluoride metabolism, leading to increased fluoride levels in their blood and reduced excretion through urine. These findings emphasized the importance of monitoring fluoride levels in patients with chronic renal failure and implementing appropriate interventions to prevent potential adverse effects associated with excessive fluoride accumulation in their bodies.

Figure 4: fluoride recommendation as per the age [Institute of Medicine, Food and Nutrition Board. 1997]



* Females (including pregnant or lactating) above the age of 18 years have same recommendation for fluoride as 14 - 18 years

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