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# Fluoride's Effects on the Human Body: Probable Risks and Possible Benefits

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## Abstract

Fluoride, naturally present in numerous foods and water sources, helps prevent tooth decay and promotes the remineralization of dental enamel. Two recent dental school graduates from the late 19th and early 20th century, Black and McKay, were the first to propose using fluoride as an effective caries prevention agent. In the past, individuals relied on the natural source of fluoride, mainly water and some foods. In some places, the fluoride level in the water was so low that it did not provide any benefits in the form of enamel protection. However, high fluoride levels in water sources cause endemic fluorosis that affects about 200 million people worldwide and is prevalent in countries such as India, Iran, Kenya, and Mexico. In the past, water fluoridation was heralded as one of the most significant public health achievements in the twentieth century for avoiding dental cavities. Since this method is neither cost-effective nor practical in many places, particularly rural ones, scientists and policymakers have studied alternative methods, such as milk or salt fluoridation, for providing fluoride to the general population. However, excessive fluoride exposure can be hazardous and lead to various illnesses, including skeletal fluorosis, muscle weakness, kidney failure, and gastrointestinal issues. This excessive fluoride consumption and toxicity prompted several nations to abolish fluoridation. Today's leading causes of poisoning are unsupervised ingestion of dental and oral hygiene products and excessive water fluoridation. Future studies should deliver a safe level of fluoride over time and give it in ways other than water fluoridation.

***Keywords:*** Hydrofluoric Acid (HF); Fluoride's Effects; Human Body; Water Fluoridation

## Introduction

### *Background: fluoride's discovery*

Even though the effects of hydrofluoric acid (HF) were known as early as 1670, fluorine was not isolated and named until more than 200 years later. The extreme reactivity of HF and its toxicity made the discovery of fluorine difficult and risky. The German mineralogist Georgius Agricola wrote about a crystalline substance that allowed some ores to melt at lower temperatures. From the Latin fleure, which means "to flow," he gave it the name fluores. Fluorspar, fluorite, calcium fluoride, and $CaF_2$ are modern names for them.

The study of the role of fluoride in improving oral health began during the first half of the twentieth century when the link between natural fluoride, adjusted fluoride levels in drinking water, and reduced dental caries was proven. In 1901, a recent dental school graduate named Frederick McKay left the East Coast to start a dental practice in Colorado Springs, USA.

This study was the beginning of fluoride research [1]. When McKay arrived, he was shocked to see many Colorado Springs residents with horrifying brown stains on their teeth. These permanent stains could be so poor that, occasionally, entire teeth would have chocolate-colored splotches. McKay searched endlessly for information on this peculiar disorder. No dental literature at that time could any reference be made to the brown-stained teeth. McKay took up the challenge and began his investigation into the situation. Most local dentists should have shown more interest in his initial epidemiological studies. After much work, McKay got local experts interested in the problem, which was then called Colorado Brown Stain.

McKay got his big break in 1909 when renowned dental researcher Dr. G.V. Black agreed to go to Colorado Springs and collaborate with him on the puzzling disease. The Grand Rapids water fluoridation study, conducted in the 1940s, was the first to use this knowledge to strengthen teeth. During the 15-year project, researchers observed the rate of tooth decay among the nearly 30,000 schoolchildren in Grand Rapids. Children in Grand Rapids who were born after water fluoridation started experiencing a 60% reduction in caries rates by the end of the study's first 11 years. Based on the positive results of this pilot study, states decided to add fluoride to the public water supply to help reduce tooth decay and improve oral health [2].

### *The deplorable history of fluorine*

Anhydrous hydrogen fluoride, which has a boiling point of 19°C, is used to make the element fluorine. Both liquid and vapor are toxic, and liquid formation is more likely to result in severe burns [3]. Sir Humphry Davy, Louis-Joseph Gay Lussac, and Louis-Jacques Thenard experienced severe side effects from HF, such as eye and fingernail injuries. Thomas Knox, Paul Louyet, and Jerome Nickles died during their investigations, presumably from the impact of inhaling HF [3].

## Discussion

### *Fluoride consumption*

One of the top 10 achievements in public health of the $20^{th}$ century is the fluoridation of drinking water [4]. Most water supplies naturally have mineral fluoride, which comes from geological sources. The US Centers for Disease Control and Prevention states that fluoridating public drinking water is a safe, inexpensive, and effective way to reduce tooth decay among Americans of all ages and income levels. Based on readings from McKay and Black's fluorosis studies, it was hypothesized that fluoride added to drinking water at both physically and aesthetically safe levels would aid in preventing tooth decay. After extensive discussions with scientists from the PHS, the Michigan Department of Health, and other public health organizations, the City Commission of Grand Rapids, Michigan, decided to add fluoride to its public water supply the following year, in 1944. Grand Rapids fluoridated its drinking water for the first time in 1945 [2].

The U.S. Surgeon General had initially sponsored the Grand Rapids water fluoridation study, which the NIDR took over shortly after the institute's founding in 1948. Almost 30 years after the conclusion of the Grand Rapids fluoridation study, fluoride remains the primary tool of dental science in the fight against tooth decay. More than 200 million Americans currently benefit from water fluoridation projects, and 13 million schoolchildren now participate in fluoride mouth rinse programs offered in schools. Fluoride is also an active ingredient in nearly every toothpaste on the market today.

As of 2012, artificial water fluoridation was practiced in some capacity in 25 countries, and more than half of the population in 11 nations consumed it. Twenty-eight more nations have naturally fluoridated water, although many have fluoride levels that are too high to be considered safe. Approximately 435 million people worldwide (or 5.4% of the world's population) had fluoridated water to the recommended level as of 2012; almost half of them reside in the United States [2].

Fluoridation can be defined as the upward or downward adjustment of the level of fluoride content in drinking water to an optimal level, just enough to prevent caries but not enough to cause fluorosis [5]. Fluoride levels of 0.5 ppm are recommended in warm climates where more water is consumed, and levels as high as 1.5 ppm are considered optimum in cold climates where less water is consumed. However, on average, the optimal fluoride level in drinking water is calibrated at 1.0 ppm worldwide (0.7 - 1.2 ppm) [5].

### *Chemical (molecular) structure of fluoride*

Fluorine is the ninth chemical in the periodic table that belongs to the halogen family. Fluoride is either a fluorine ion or a compound containing fluorine. A fluoride ion (chemical formula F, atomic number 9) is the simplest inorganic monatomic anion found in nature. It is considered a trace element (Figure 1). Fluoride is a negatively charged ion with 9 protons and 10 electrons, and the electronic configuration of the valence shell is $2s^2$ and $2p^6$.

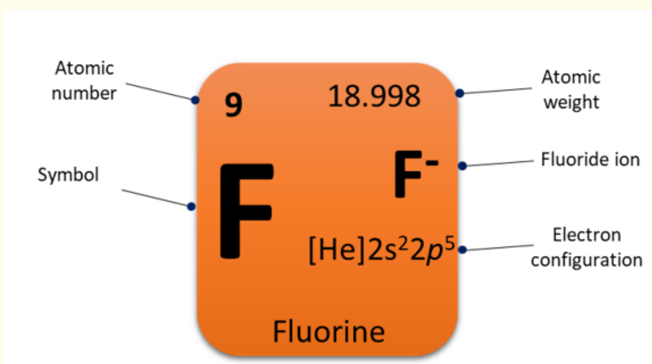


***Figure 1:*** *Chemical characteristics of fluoride*

### *Fluoride metabolism in the body*

pH affects fluoride metabolism, including how it passes through the stomach and exits the body through the kidneys [6]. When there is a difference in pH between 2 compartments of body fluids adjacent to each other [7], fluoride can easily pass through cell membranes as HF. Fluoride levels in the blood rise rapidly after ingestion because the stomach absorbs them quickly. The small intestine absorbs most of the fluoride that the stomach cannot absorb. Fluoride, taken in, is passed out of the body in the feces. Plasma maximum fluoride levels are reached 20 - 60 minutes after ingestion [8]. The main reasons the level drops after that are that the calcified tissues absorb it, and urine is absorbed by it. Many factors can modify the metabolism and effects of fluoride in the organism, such as chronic and acute acidbase disturbances, hematocrit, altitude, physical activity (Figure 2), circadian rhythm and hormones, nutritional status, diet, and genetic predisposition [6,9].

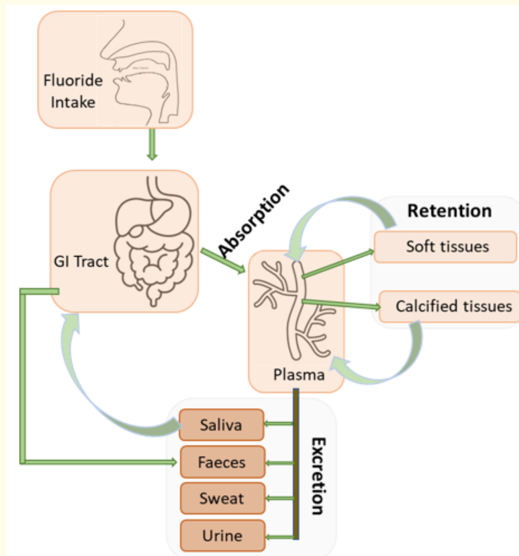


***Figure 2:*** *Fluoride metabolism*

### *Mechanisms of action of fluoride for the control of caries*

Fluoride consumption has good and bad effects, such as lowering the number of dental cavities and causing skeletal fluorosis after a long period of high exposure [10]. The intake ranges that produce these opposing effects are close. In the 1980s, fluoride's topical effect was found to be the primary way it stops cavities. When present in low and steady concentrations (range sub-ppm) in oral fluids, fluoride can adhere to the surface of apatite crystals during the acidic challenge and stop demineralization [11].

When fluoride-rich solutions are placed on the teeth, calcium fluoride ($CaF_2$) falls out, forming free fluoride ions. These free fluoride ions store fluoride during demineralization and remineralization. The nucleating action of the partially dissolved minerals creates a mineral that prefers fluoride over carbonate. This nucleating action makes enamel more resistant to acidic problems in the future. When the pH is returned to normal, small amounts of fluoride in the solution, make it very saturated with fluorhydroxyapatite (FHAP or FAP), speeding up the remineralization process [11].

When the pH is returned to normal, small amounts of fluoride in the solution, make it very saturated with fluorhydroxyapatite (FHAP or FAP), speeding up the remineralization process [11]. When fluoride interacts with the mineral that makes up teeth, it replaces OH- with F- to form fluorohydroxyapatite [12]. Overall, the solubility decreases, hydrogen bonds become more robust than before, and the density of the crystal lattice increases as a result. We rarely exceed several thousand parts per million of fluoride in the outer enamel, but as fluoride incorporation levels increase, so does the decrease in solubility [13]. Therefore, only limited protection against fluoride substitution would be expected compared to pure FAP, which has 40,000 ppm fluoride. Ion exchange and topical applications are other ways to add fluoride to the enamel.

### *Body storage of fluoride*

Fluoride is a toxin that builds up in the body over time [14]. The kidneys only remove a small portion of fluoride after consumption, and the rest is free to roam in the body. The body eventually stores fluoride in 4 significant locations: teeth, bones, brain, and pineal gland, after ingesting it and moving around the body [14]. Fluoride causes considerable harm and has several adverse effects on one's health as it accumulates in these areas of the body.

### *Traditional application of fluoride*

Due to its role in the mineralization of bones and teeth, which contain more than 99% of the total fluoride content of the body [15], fluoride significantly impacts nutrition and public health.

**Cariostatic effect:** The use of fluorides has dramatically reduced dental decay over the past decades, and, as a public health measure, fluoride still plays a valuable role in improving the oral health of communities [16]. Fluoride strengthens teeth and reduces the risk of cavities by approximately 25%. Fluoride remineralizes tooth enamel explicitly, stops early tooth decay, slows demineralization, and stops the bacteria that cause cavities to grow.

**Bone effect:** The actions of fluoride on bones appear to be through its physicochemical effects on bone crystals and its biological effects on bone cells [17]. Fluoride is one of the few ions known to increase bone cell growth (osteoblasts) and the deposit of new minerals in cancellous bone [15]. Fluoride can help support bone remodeling. Fluoride may help protect against osteoporosis by stimulating osteoblast activity and inhibiting osteoclast activity, which plays a role in postmenopausal osteoporosis [18,19]. A meta-analysis of 25 studies on bone mineral density and fluoride supplements found increased spine and hip bone density with longer treatments with fluoride supplements but no significant effects on fracture reduction [20]. Long-term treatment with NaF has a positive effect on the density of trabecular bone.

**Anticarcinogenic effect:** Recently, it was found that fluoride salt sodium (NaF) caused tumor cell lines to undergo apoptosis. Human gingival fibroblasts, leukemia cells, hippocampus, and liver cells all experienced reduced cell viability when exposed to NaF *in vitro*, and this effect was dose and time-dependent [21,22]. Surprisingly, only one study has focused on the cytotoxicity of fluoride caused by apoptosis in bone cells [23,24]. It is currently unknown whether NaF acts intra- or extracellularly, as well as the intracellular target molecule of each fluoride compound. To fully understand the cytotoxicity caused by fluoride-induced apoptosis, doing more research using different endpoints and testing the function of cell cycle regulatory proteins is important.

### *Natural sources of fluoride*

A naturally occurring mineral called fluoride is released from rocks into the soil, water, and air [25]. The main ways people get fluoride are from toothpaste (if young children swallow it), drinks and foods made with water that has been fluoridated, prescription fluoride supplements (like tablets or drops), and other dental products (like mouthwashes, gels, and foams) [25]. Spinach, grapes, raisins, wine, black tea, and potatoes are additional foods containing fluoride [25]. Depending on the type of tea and its source, brewed tea often has higher fluoride levels than most foods [22]. This higher fluoride level is because tea plants absorb fluoride from the soil. Fluoride concentrations in brewed tea made with distilled water can range from 0.07 to 1.5 mg per cup to 0.3 to 6.5 mg/L [26].

### *Familiar sources of fluoride intake and ways to limit fluoride's intact or absorption*

Fluoride concentrations vary in different sources, such as breast milk (< 0.002 to 0.01 mg/L), cow's milk (0.007 to 0.086 mg/L), milk-based infant formula (< 0.2 mg/L), and soy-based infant formula (0.2 to 0.3 mg/L) [26]. Most kinds of toothpaste sold on the market contain fluoride in the form of sodium fluoride or monofluorophosphate, most commonly at a level of 1,000 to 1,100 mg/L (about 1.3 mg in a quarter teaspoon, a typical amount of toothpaste used for one brushing) [26]. Topical fluoride preparations are applied in dentist offices or through school-based programs and dental devices (e.g. orthodontic bracket adhesives, glass ionomer, composite resin dental restorative materials, dental sealants, and cavity liners) [27].

Excessive fluoride intake is usually caused by drinking naturally fluoridated groundwater, especially in warm climates where water use is greater, or by using water with many fluorides to cook food or water crops. We can reduce the fluoride intake of these everyday products following proactive tips (Figure 3) [28].

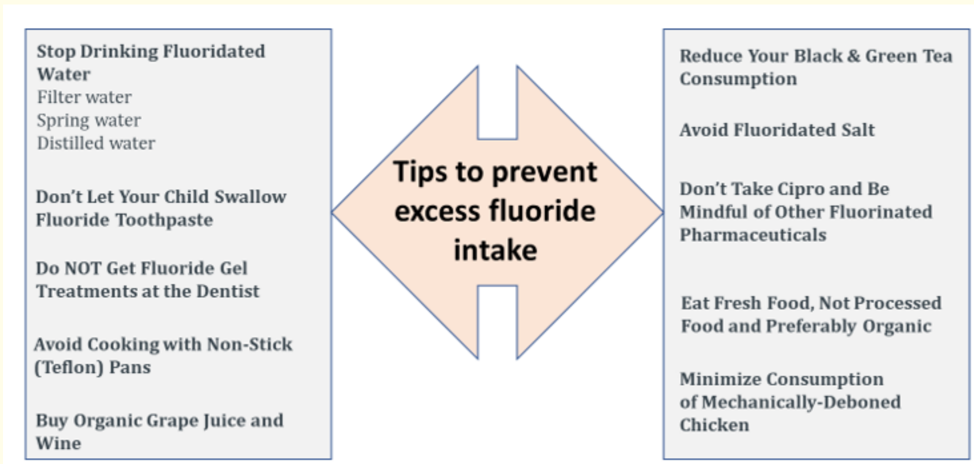


***Figure 3:*** *Adverse effects of overexposure to fluoride*

### *Adverse health conditions of fluorosis*

Excess amounts of fluoride ions in drinking water can cause dental fluorosis, skeletal fluorosis, arthritis, bone damage, osteoporosis, muscle damage, fatigue, joint-related problems, and chronicle problems [29,30]. Fluorosis is a condition that results in white or brown speckles on the teeth. Fluoride overexposure during the first years of a child's life, when permanent teeth are developing, is the cause. A surplus of fluoride can lead to a bone disease known as skeletal fluorosis [31]. Over many years, this excess can cause pain and damage to bones and joints. The bones may become more rigid and less elastic, increasing the risk of fractures [31]. Fluoride is also associated with toxicity in the developing brain, which could lead to a lower intelligence quotient (IQ), autism, and hardening of the pineal gland [32].

Excess fluoride can damage the parathyroid gland.This damage can cause hyperparathyroidism, the uncontrolled release of parathyroid hormones, the loss of calcium from bone structures, making them more likely to break, and higher calcium levels than normal in the blood [33]. The acute dose of fluoride that could result in severe systemic toxicity is 5 mg/kg, or 375 mg, for a person weighing 75 kg [34]. Excess exposure to fluorosis also leads to gastric and muscular symptoms (Figure 4).

### *Mechanism of fluoride toxicity*

Fluoride inhibits the activity of antioxidant enzymes such as catalase, glutathione peroxidase (GPx), GSH reductase (GR), and superoxide dismutase (SOD).

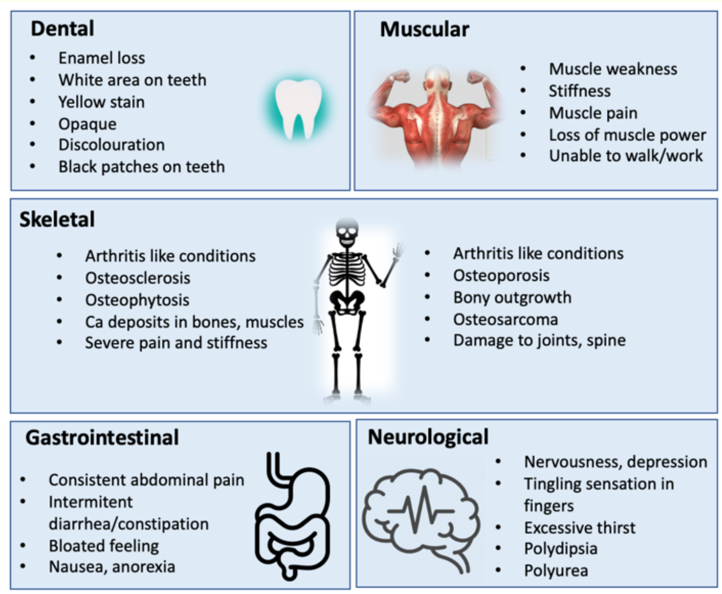


***Figure 4:*** *Toxicity symptoms of fluoride toxicity*

There are 5 main ways fluoride can be harmful: inhibition of proteins, oxidative stress, disruption of organelles, a change in pH, and electrolyte imbalance [35].

**Protein inhibition:** Fluoride, at a concentration of 0.01%, significantly reduces the anaerobic metabolism of glucose. Since $Mg^{2+}$ activates more than 300 human enzymes, fluoride competes with it and stops it from working [36]. A fluoride ion is a potent and specific inhibitor of cytoplasmic PPases. More than 200 different enzyme reactions produce intracellular PPi, and its hydrolysis is a significant catalyst for many crucial biochemical processes [37].

**Oxidative stress:** According to some authors, oxidative stress is the primary mechanism causing fluoride toxicity [37]. Fluoride increases ROS production, such as hydrogen peroxide ($H_2O_2$), superoxide anion, and reactive hydroperoxides (ROOH). Fluoride exposure can lower the GSH level in cells, frequently leading to excessive ROS production [38].

**pH and electrolyte imbalance:** At single and multicellular levels, exposure to fluoride causes acidification and electrolyte imbalance [39]. Regardless of how it happens, electrolytes fall out of balance when organisms are exposed to fluoride. This situation can cause problems with cell homeostasis and signaling. Fluoride exposure is also associated with a decrease in intracellular pH. Fluoride is a weak acid that enters cells as HF and dissociates, thus releasing one proton per fluoride [40]. Consequently, the more fluoride enters a cell, the more acidic the cytoplasm becomes.

**Cell organelle damage:** Prolonged exposure to high fluoride levels leads to widespread organelle damage. This damage is time- and concentration-dependent. Fluoride can damage the cell surface, mitochondria, endoplasmic reticulum, Golgi, and nucleus [35]. The sensitivity of each organelle to fluoride varies slightly from one organism to the next.

### *Water fluoridation*

Grand Rapids, Michigan, was the first to add fluoride to its city water system in 1945 to provide residents with the advantages of fluoride. Community water fluoridation determines how much fluoride should be added to the water supply to prevent cavities from forming. Since then, numerous cities have begun to use fluoride in community water. Almost 73% of Americans with access to community water systems in 2018 could drink fluoridated water [41], as tooth decay has decreased significantly in the past 75 years. As a result, the CDC named community water fluoridation one of the top 10 public health achievements of the twentieth century. The U.S. Environmental Protection Agency (EPA) is investigating the maximum amount of fluoride in drinking water. The current standard must be followed is 4.0 mg/L, which is meant to stop severe skeletal fluorosis [42]. In 2012, more than 435 million people worldwide had access to naturally fluoridated water (about 57 million) or water with adjusted fluoride concentrations at or near optimal levels (about 378 million). These countries include the United States, Brazil, Australia, Canada, Spain, Argentina, South Korea, and New Zealand [43]. The only European countries that fluoridate their water are Ireland, Poland, Serbia, Spain, and the UK.

However, most developed nations, including Japan and 97% of Europeans, do not drink fluorine-containing water [44]. India, China, and parts of Africa have areas with elevated levels of natural fluoride in their water and are taking measures to remove fluoride [44]. Fluoridation has been debated in recent years, and several countries are taking measures to reduce fluoride intake due to its risk of toxicity and many other concerns.

Although fluorinating drinking water is the most popular public health measure to prevent cavities, some countries also fluoridate milk and salt. The concept of milk as a fluoride vehicle emerged in the early 1950s and was first investigated almost simultaneously in Switzerland, the U.S., and Japan [45,46]. Since 1986, programs aimed at validating the feasibility of community use of fluoridated milk for caries prevention have been promoted and supported by the WHO International Program for Milk Fluoridation [45]. Currently, milk fluoridation programs, supported by the WHO and the Food and Agriculture Organization, are running continuously in about 15 countries, and various channels are used to provide fluoridated milk to children attending kindergarten and school. Although adding fluoride to milk is a simple process, milk fluoridation is a less efficient method of fluoride delivery because fluoride added to milk forms insoluble complexes that make fluoride absorption difficult [45].

### *Other medical prescriptions*

Researchers think fluoride supplements might reduce the risk of bone fractures, but not much evidence supports this view. Clinical trials and observational studies had conflicting findings on the efficacy of fluoride dietary supplements in preventing bone fractures [47-50].

### *Political and public health factors affecting fluoridation*

Because fluoridation of public drinking water systems effectively reduced dental caries, PHS provided recommendations on optimal fluoride concentrations in drinking water for community drinking water systems in 1962 [51,52]. The U.S. Department of Health and Human Services (HHS) is releasing this updated PHS recommendation because of new data about changes in the prevalence of dental fluorosis, the relationship between children's water intake and the temperature outside, and how much fluoride in drinking water contributes to total fluoride exposure in the U.S. Even though the PHS says that fluoridating public water systems is an excellent way to improve public health, the decision to do so is made by state and local governments. The plans of Brazil and Colombia for the use of fluoride began to be different in terms of public policy options for the use of systemic fluoride. In Brazil, the alternative was to adjust the fluoride concentration in the water, while in Colombia, adding fluoride to table salt was consolidated as a public policy [53].

### *Future perspective*

Fluorinating community water supplies is a secure and reliable way to reduce dental caries. Fluoridated salt, water, and fluoride supplements in food have been shown in many studies to be effective ways to prevent cavities. Because topical fluorides have significantly dropped cavities in many developed countries, the absolute number of cavities will decrease much less when systemic fluoride is used. Community fluoridation is the most sensible course of action from the perspective of cost-effectiveness and the overall impact of caries prevention in countries where most of the population lives in cities with communal water supplies [54].

The recommendation for dietary fluoride supplements is limited to areas where neither water fluoridation nor salt fluoridation is possible or as a temporary measure. Despite differing opinions on the relative caries prevention effects of pre- and post-eruptive systemic fluoride methods to prevent dental caries, their validity remains unchallenged. Recent clinical and epidemiological studies will affect how these techniques are developed. The importance of social, political, economic, and educational factors will be on par with or even more significant. Future use of fluorides is suggested, emphasizing that water fluoridation is a proven and safe health measure that should be maintained. Fluoride supplementation through additional means is discouraged, particularly when it comes to compliance and the use of fluoride supplements that are under the control of the individual. Fluorides and other preventive measures for dental health should be aimed at children who could benefit from them.

## Conclusion

Fluoride is an element that is constantly present in the environment and people's daily lives. Dietary intake, breathing, and fluoride supplements can expose people to these substances. Fluoride protects teeth from decay by promoting demineralization and remineralization. Too much fluoride can lead to dental or skeletal fluorosis, damaging bones and joints. Appropriate water fluoridation levels help achieve a better risk-benefit ratio for fluoride consumption.

## Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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**Volume 6 Issue 8 August 2023**