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# Critical analysis of the use of fluoride in Public Health: controversies and evidence

Francisco Miguel Silva Salgado

Dissertação conducente ao Grau de Mestre em Ciências Farmacêuticas (Ciclo Integrado)

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# Critical analysis of the use of fluoride in Public Health: controversies and evidence

Trabalho realizado sob a Orientação de
Cristina Maria Cavadas Morais Couto

# DECLARATION OF INTEGRITY

I, duly identified above, declare, for all due purposes, that this work is original, was prepared by me, and is the result of my own personal effort, having been developed with absolute integrity.

I further declare that this work has not been previously submitted, in whole or in part, for any other academic purpose and that, throughout its preparation, I did not resort to any form of result falsification or plagiarism; all sources consulted and third-party contributions are duly identified and referenced throughout the text, in accordance with the applicable academic and scientific standards.

I also declare that any similarity with other works, whether published or not, is purely coincidental or the result of properly indicated citation.

## Contribution of work to sustainable development goals established by the United Nations

This work falls under different United Nations Sustainable Development Goals (SDGs) due to its focus on the safe regulation and environmental monitoring of fluoride as a public health intervention.

- **SDG 6 – Clean water and sanitation:** the dissertation focuses on the necessity of monitoring and regulating fluoride concentrations in drinking water to ensure safe consumption and prevent endemic health issues like fluorosis. Groundwater fluoride levels are highly dependent on geological and mineral characteristics, requiring precise management of water resources.
- **SDG 11 – Sustainable cities and communities:** the study supports the development of healthy communities by advocating for risk-stratified health strategies that balance population-level benefits with individualized risk mitigation. This ensures that public health measures are equitable and sensitive to the specific needs of different demographic groups.
- **SDG 13 – Climate action:** the dissertation emphasizes that environmental factors and water scarcity can influence the concentration of naturally occurring fluoride in groundwater, potentially increasing the risk of over-exposure. The promotion of sustainable water treatment methods is therefore essential for climate change adaptation and protecting vulnerable populations.
- **SDG 14 – Protect marine life:** one of the concerns of the work is the ecotoxicity of fluoride and the risks associated with its release into aquatic environments. By analyzing the systemic distribution and environmental presence of fluoride, the dissertation contributes to the preservation of marine ecosystems and aquatic biodiversity through advocating for improved containment and regulatory strategies.

## Resumo

**Introdução:** O fluoreto ($F^-$) é um agente farmacologicamente ativo essencial para a saúde dentária, atuando através do aumento da remineralização e da inibição da desmineralização via formação de fluorapatite resistente aos ácidos. Embora seja considerado como um dos maiores sucessos de saúde pública do século XX, a sua aplicação sistémica através da fluoretação da água enfrenta atualmente um escrutínio científico e ético significativo. **Objetivo:** Esta dissertação fornece uma análise crítica, baseada na evidência, do papel do fluoreto na saúde pública, equilibrando a sua eficácia terapêutica com a potencial toxicidade. **Métodos:** Foi realizada uma pesquisa bibliográfica sistemática nas bases de dados PubMed, ScienceDirect e PubChem, com foco nas propriedades físico-químicas, farmacocinética e resultados clínicos do fluoreto. **Resultados:** A distribuição do fluoreto concentra-se principalmente nos tecidos calcificados (99%), incluindo ossos e dentes. A sua absorção é dependente do pH ocorrendo principalmente como fluoreto de hidrogénio por difusão passiva. A investigação atual destaca uma janela terapêutica estreita: enquanto doses ideais previnem a cárie, a ingestão crónica superior a 0,1 mg/kg/dia leva à fluorose dentária e esquelética. Avaliações recentes de 2024-2025 da EFSA e do Programa Nacional de Toxicologia dos EUA sugerem potenciais riscos no neurodesenvolvimento, incluindo pontuações de QI mais baixas em crianças expostas a concentrações na água superiores a 1,5 mg/L. **Conclusão:** Observa-se uma transição global para a administração tópica de fluoreto, que oferece uma redução significativa da cárie com menor risco sistémico. Os profissionais das ciências farmacêuticas e de saúde pública devem conciliar os benefícios ao nível populacional com a mitigação de riscos individualizada e considerações éticas relativas à medicação em massa.

**Palavras-chave:** Fluoreto; Saúde Pública; Cárie Dentária; Neurotoxicidade; Fluorose; Farmacocinética; Microbioma, Avaliação de Risco

## Abstract

**Introduction:** Fluoride ($F^-$) is a pharmacologically active agent essential for dental health, functioning by enhancing remineralization and inhibiting demineralization through the formation of acid-resistant fluorapatite. While hailed as a major 20th-century public health success, its systemic application through water fluoridation currently faces significant scientific and ethical scrutiny. **Objective:** This dissertation provides a critical, evidence-based analysis of fluoride's role in public health, balancing its therapeutic efficacy against potential toxicity. **Methods:** A systematic literature search was conducted using PubMed, ScienceDirect, and PubChem, focusing on fluoride's physicochemical properties, pharmacokinetics, and clinical outcomes. **Results:** Fluoride distribution is primarily concentrated in calcified tissues (99%), including bones and teeth. Its absorption is pH-dependent, occurring mainly as hydrogen fluoride via passive diffusion. Current research highlights a narrow therapeutic window, while optimal doses prevent caries, chronic intake exceeding 0.1mg/kg/day leads to dental and skeletal fluorosis. Recent 2024-2025 assessments from the EFSA and National Toxicology Program suggest potential neurodevelopmental risks, including lower IQ scores in children exposed to water concentrations above 1.5 mg/L. **Conclusion:** There is a global shift toward topical fluoride delivery, which offers significant caries reduction with lower systemic risk. Pharmaceutical and public health professionals must reconcile population-level benefits with individualized risk mitigation and ethical considerations regarding mass medication

**Keywords:** Fluoride; Public Health; Dental Caries; Neurotoxicity; Fluorosis; Pharmacokinetics; Microbiome, Risk Assessment.

# Acknowledgements

First and foremost, I would like to express my deepest and most sincere gratitude to my supervisor, Professor Cristina Couto. Her guidance, scientific expertise and constant encouragement were fundamental to the successful completion of this dissertation. I am truly grateful for her patience and for the pivotal role she played in helping me navigate the complexities of this research, ensuring that I could reach this final stage with academic rigor and confidence.

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# List of Abbreviations, Acronyms and Initialisms

**ATSDR-** Agency for Toxic Substances and Disease Registry

**BMDL-** Benchmark Dose Level (Lower Bound)

**DALYs-** Disability-Adjusted Life Years

**DNA-** Deoxyribonucleic Acid

**EFSA-** European Food Safety Authority

**EPA-** Environmental Protection Agency

**EU-** European Union

**$F^-$-** Fluoride ion

**$F_2$-** Elemental fluorine

**HF-** Hydrogen fluoride

**iNOS-** inducible Nitric-Oxide Synthase

**IQ-** Intelligence Quotient

**MAPK-** Mitogen-Activated Protein Kinase

**MIREC-** Maternal-Infant Research on Environmental Chemicals study

**NHANES-** National Health and Nutrition Examination Survey

**OS-** Oxidative Stress

**PET-** Positron Emission Tomography

**pKa-** Acid dissociation constant

**ppm-** parts per million

**$Sn^{2+}$-** Stannous ion

**$SnF_2$-** Stannous fluoride

**UHC-** Universal Health Coverage

**WHO-** World Health Organization

# 1. Introduction

From a pharmaceutical and public health standpoint, fluoride is not just a nutrient, it acts as a pharmacologically active agent that when applied systemically or topically promotes tooth remineralization and prevents demineralization. This pharmacological relevance is intrinsically linked to its unique chemical properties, which allow for its effective, controlled application and incorporation into public health measures.

Fluoride ($F^-$), a monatomic anion of fluorine, is widely distributed in the environment, naturally occurring in rocks, soil, and water, and constitutes approximately 0.08% of the Earth's crust (1). The primary action of fluoride in the human body, particularly at lower concentrations, involves its incorporation into calcified tissues, such as bones and teeth. In dental health, fluoride replaces hydroxyl ions in the hydroxyapatite crystals of tooth enamel, forming fluorapatite (2). This fluorapatite is more resistant to acid demineralization, thereby strengthening the enamel and making teeth more resilient to decay caused by bacterial acids (3,4). Given this fundamental role, the use of $F^-$ for decreasing the prevalence and incidence of tooth decay, was the greatest worldwide preventive public health measure of the 20$^{th}$ century.

However, the widespread use of fluoride, particularly in public drinking water, has become a nexus of persistent scientific debate, ethical controversy and public scepticism. While the anti-caries efficacy of optimally dosed fluoride is supported by a vast body of epidemiological and clinical evidence, concerns regarding potential adverse effects have fuelled ongoing contention.

The critical analysis of fluoride use in public health represents a pivotal research nexus within pharmaceutical and health sciences, bridging evidence-based therapeutics, public policy and ethical healthcare delivery. From a pharmaceutical perspective, fluoride exemplifies the complex interplay between therapeutic efficacy and toxicity, a paradigm where precise dosing determines whether it functions as a vital public health tool or a developmental toxicant (5,6).

Pharmacists routinely engage with this duality through dispensing fluoridated products and advising on risk-stratified usage, particularly for vulnerable populations like children and renal-impaired patients who face heightened fluorosis risks (2,6).

Ultimately, this domain challenges pharmaceutical and public health professionals to reconcile population-level benefits with individualized risk mitigation, a task requiring rigorous evidence synthesis, interdisciplinary collaboration and ethical vigilance to optimize oral health outcomes while minimizing iatrogenic harm (7,8).

## 2. Aim and scope of the dissertation

Fluoride stands at the fascinating intersection of public health success story and ongoing scientific controversy, making it one of the most compelling subjects for pharmaceutical research today. What makes $F^-$ particularly worthy of rigorous pharmaceutical scrutiny is its unique status as both an essential preventive agent and a potential toxic substance, depending entirely on dosage and delivery method. The very same chemical properties that make fluoride so effective at preventing dental caries is the ability to integrate into tooth enamel and inhibit demineralization but also raise important questions about long-term accumulation in the body and potential systemic effects. The primary aim of this study is to transcend polarized debates through a critical, evidence-based examination, and an up-to-date review of fluoride's role in population health.

## 3. Material and Methods

The literature search for this dissertation was conducted using a structured and systematic methodology designed to identify a comprehensive range of scientific evidence. Research was primarily executed through the PubMed and ScienceDirect electronic databases, with the PubChem database utilized for obtaining precise chemical identifiers and nomenclature for the compounds of interest. The search was primarily focused on articles published in English between 2014 and 2025 to ensure the inclusion of the most recent clinical evidence, international risk assessments, and emerging toxicological data. However, foundational pharmacological and toxicological texts published prior to this window were also incorporated to provide the necessary historical and mechanistic context.

The search strategy utilized tailored keywords and controlled vocabulary specific to each database's indexing system. In PubMed, Medical Subject Headings terms such as "Fluoridation," "Fluorides, Topical/adverse effects," and "Dental Caries/prevention and control" were integrated with free-text keywords including "fluoride controversy,"

"neurotoxicity," and "skeletal fluorosis". In ScienceDirect, key phrases were linked to refine the search results, specifically targeting "water fluoridation," "public health," "fluoride exposure," and "cognitive effects".

Retrieved articles were screened against pre-defined inclusion and exclusion criteria to maintain high scientific standards. Inclusion criteria prioritized systematic reviews, meta-analyses, and prospective longitudinal cohort studies. Exclusion criteria were applied to non-peer-reviewed articles, editorials and studies exclusively involving animal models, except in cases where such models provided essential insights into fundamental toxicological mechanisms. The selection process involved a two-phase assessment, an initial screening of titles and abstracts, followed by a comprehensive full-text review to identify the most pertinent studies for final analysis.

## 4. Results and Discussion

### 4.1. Fluoride- major physicochemical characteristics

Fluoride is a naturally occurring ion widely distributed throughout the Earth's crust and various water sources. Geologically, fluoride is found in numerous minerals, contributing to its pervasive presence in the environment. The Earth's crust naturally contains approximately 0.08% fluoride (1,8). This widespread occurrence stems from fluoride's presence in minerals such as fluorite ($CaF_2$), fluorapatite ($Ca_5(PO_4)_3F$), and cryolite ($Na_3AlF_6$) (9). Also, fluoride is found in all natural waters at different concentrations. Seawater typically contains about 1 mg $L^{-1}$, while rivers and lakes generally exhibit concentrations of less than 0.5 mg $L^{-1}$. In groundwater $F^-$ concentration is dependent on the nature of the rocks and the occurrence of fluoride-bearing minerals (10).

Fluorine, considered as a trace element, is the lightest member of the halogen group and is one of the most reactive of all chemical elements. It is the most electronegative of all the elements which means that it has a strong tendency to acquire a negative charge and in solution forms $F^-$ ions. It is not, therefore, found as fluorine in the environment. Other oxidation states are not found in natural systems, although uncharged complexes may be.

Fluoride ions have the same charge and nearly the same radius as hydroxide ions and may replace each other in mineral structures. Fluoride forms mineral complexes with a few cations, and some common mineral species of low solubility contain fluoride (1) .

The fluoride ion is the biologically active central form used in public health interventions, distinct from highly reactive elemental fluorine ($F_2$), presenting basic properties (11,12).

### 4.2. Distribution and fate in human organism – deficiency and excess

Fluoride behavior in biological systems, including its specific interactions with the dental enamel surface, is critically governed by its physicochemical properties (Figure 1) (11,13). Its metabolism, including gastric absorption, distribution and renal excretion are pH dependent. In acid environments, it readily forms uncharged hydrogen fluoride (HF) which is a weak acid with a $pK_a$ of 3.4. Thus, at pH 3.4, 50% of fluoride is in the undissociated form, while the remaining 50% is in the dissociated or ionic form ($F^-$) and as pH decreases the concentration of HF increases and the concentration of $F^-$ decreases.

The coefficient of permeability of lipid bilayer membranes to HF is 1 million times higher than that of $F^-$ (this means that $F^-$ crosses cell membranes as HF in response to a pH gradient between adjacent body fluid compartments) (11).

In the absence of high amounts of bi and trivalent cations (eg. calcium, aluminium and magnesium) that may complex $F^-$ and form insoluble compounds, approximately 80 to 90% of the ingested $F^-$ is absorbed from the gastrointestinal tract. Fluoride absorption occurs by passive diffusion and is not affected by temperature changes or metabolic inhibitors.

Fluoride absorption occurs rapidly, with a half-time of approximately 30 min, and unlike most substances, roughly 20 to 25% of the total $F^-$ ingested is absorbed from the stomach, while the remainder is absorbed from the proximal small intestine (11).

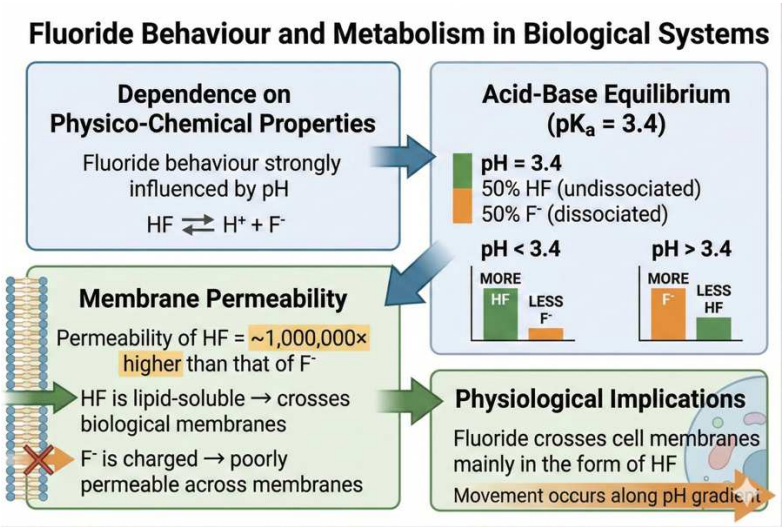


*Figure 1- Fluoride behaviour and metabolism, Adapted (11).*

After absorption, $F^-$ is rapidly distributed throughout the organism. Plasma $F^-$ levels start to increase within 10 minutes following $F^-$ intake and peak concentrations are reached within 20 to 60 minutes. From a pharmacokinetic point of view, plasma is regarded as the central compartment for $F^-$ distribution, since it is the fluid from which and into which fluoride must pass to be distributed to hard and soft tissues and excreted. A small part (<1%) of absorbed $F^-$ is found in soft tissues, where a steady-state distribution between extracellular and intracellular fluids is established (11). The largest concentration of $F^-$ in the body is found in calcified tissues. Approximately 99% of the $F^-$ in the body is found in bones and teeth and in the pineal gland which contains hydroxyapatite who also accumulates $F^-$. Fluoride is incorporated into bone by replacing the hydroxyl ion in hydroxyapatite to form hydroxyfluoroapatite, however $F^-$ is not irreversibly bound to bone and is mobilized from bone through the continuous process of bone remodelling and to a lesser extent from ionic flux between interstitial $F^-$ and the crystalline bone surface (Figure 2) (12).

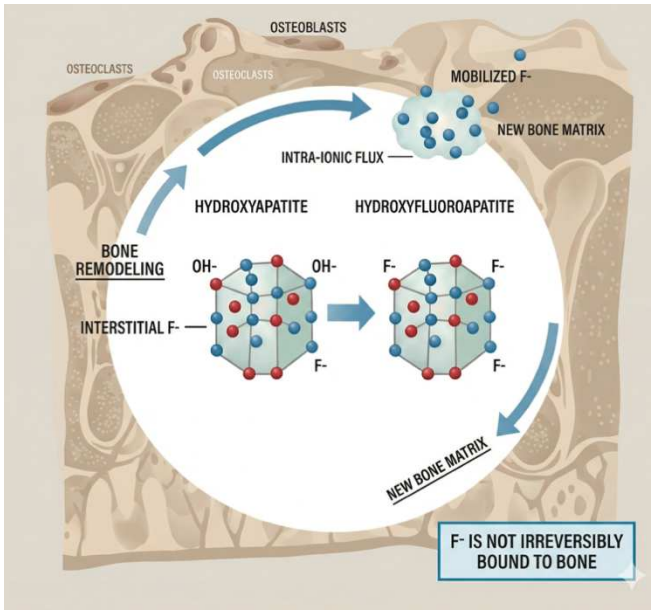


*Figure 2- Fluoride Dynamics in Bone Tissue, Adapted from ATSDR (12) and Whitford (11)*

Fluoride is either retained in soft tissues or calcified tissues or excreted through saliva, faeces, sweat or urine. The kidneys filter the plasma and excrete fluoride into the urine regulating the body's fluoride balance (2). Renal excretion occurs, approximately 90% is pH-dependent, with acidic urine reducing clearance and increasing retention.

$F^-$ lacks essential biological function and no deficiency syndrome exists, however, epidemiological evidence confirms that an intake <0.01 mg/kg/day significantly elevates caries risk due to inadequate enamel remineralization. Conversely, chronic excess (>0.1 mg/kg/day) overwhelms skeletal storage capacity, inducing dose-dependent pathologies: early-stage dental fluorosis and progressive skeletal fluorosis at intakes >6–14 mg/day for ≥10 years (1,11,12,14) .

Acute fluoride toxicity represents a medical emergency characterized by a rapid onset of life-threatening symptoms following ingestion of ≥5 mg $F^-$/kg body weight. The pathophysiology involves three primary mechanisms: precipitation of ionized calcium by absorbed fluoride, inducing hypocalcaemia and subsequent cardiac instability, inhibition of key mitochondrial enzymes disrupting cellular respiration and direct corrosive action on gastrointestinal mucosa (1,11,12,14).

Fluoride interacts with other environmental factors such as hard water, heavy metals and toxins, that can lead to several physiological responses, including the activation of inducible nitric-oxide synthase (iNOS), other cytokines, and enzymes, which in turn result in increased inflammation and excessive oxidative stress (OS). Consequently, this excessive OS leads to renal tubular necrosis and fibrosis, representing significant pathological changes in the kidneys (15).

Fluoride exposure can lead to alterations in gene expression, affecting signalling pathways, epigenetic modifications and ultimately cellular function and organismal health (16,17). For instance, $F^-$ has been shown to activate the mitogen-activated protein kinase (MAPK) pathway which plays a crucial role in regulating gene expression. It is known to inhibit several enzymes, including phosphatases and kinases. These enzymes play important roles in regulating cellular processes, including gene transcription. By inhibiting these enzymes, $F^-$ can alter the phosphorylation status of transcription factors and other regulatory proteins. Fluoride can also affect epigenetic modifications, such as DNA methylation and histone acetylation. These modifications can alter the accessibility of DNA to transcription factors, thereby influencing gene expression. Although the precise mechanisms by which $F^-$

affects epigenetic modifications are not fully understood, it is plausible that it can influence gene expression by altering the epigenetic landscape of cells.

These effects can vary depending on the concentration of $F^-$, the cell type and the specific genes being studied. While some studies have shown that $F^-$ can alter gene expression, others have found no significant effects (15,17).

### 4.3. Historical context of fluoride uses in dentistry and public health

Oral health is fundamental to overall well-being, influencing essential functions such as communication, facial expressions, sensory perception (taste and smell), touch, mastication, swallowing and the ability to express emotions without craniofacial discomfort or pain (18).

The public health intervention of community water fluoridation originated from early 20$^{th}$ century observations by Dr. Frederick McKay, who linked mottled enamel (fluorosis) to a paradoxical resistance to dental caries (1,5). Subsequent research, by Dr. H. Trendley Dean, established a causal relationship with $F^-$ and identified an optimal concentration of approximately 1.0 ppm to maximize caries prevention while minimizing aesthetically insignificant fluorosis (1,5). Pioneering trials in the U.S. and Canada (1945-46) demonstrated a dramatic reduction in dental caries, up to 60%, among children, leading to an early endorsement by major U.S. health authorities (1,5). This successful adoption positioned water fluoridation as a model public health strategy, later endorsed by the World Health Organization (WHO). Despite this initial global influence, this practice is now limited. While over 30 nations have implemented fluoridation policies, several, citing concerns over safety and efficacy, have since discontinued them. Consequently, only a small fraction (5%) of the global population currently consumes artificially fluoridated water, reflecting ongoing international debate surrounding this intervention (1,2,5-7).

### 4.4. The role of fluoride in preventing dental caries

Fluoride's role in preventing dental caries is multifaceted, primarily involving the enhancement of enamel remineralization and the inhibition of demineralization. These processes contribute to the formation of fluorapatite, a more acid-resistant crystal, within the tooth enamel. $F^-$ integrates into the hydroxyapatite structure of enamel, transforming it into fluorapatite, which is less susceptible to acid dissolution (Figure 2). This

transformation is crucial in preventing the initiation and progression of dental caries. The presence of $F^-$ in saliva also aids in the remineralization of enamel lesions, reversing early signs of tooth decay. Furthermore, $F^-$ can interfere with the metabolic activity of cariogenic bacteria, reducing their ability to produce acids (2,19).

### 4.5. Recommended intake levels

Based on the European Food Safety Authority's (EFSA) updated risk assessment, fluoride exposure in the European Union (EU) does not pose a major health concern for the general population (Table 1). The expert panel established a safe level of intake of 3.3 mg/day for pregnant women and all individuals aged nine and above, a threshold protective against potential adverse effects on the fetal nervous system, bones and thyroid. Importantly, this safe level is not exceeded under normal conditions, as fluoride concentrations in EU drinking water are typically well below the legal limit of 1.5 mg/L (20).

Table 1 - *Adequate intake per day of $F^-$ according to age, recommended by EFSA (20).*

| POPULATION GROUP | ADEQUATE INTAKE |
|---|---|
| CHILDREN (0-12 MONTHS) | 1.0 mg |
| CHILDREN (1-3 YEARS) | 1.6 mg |
| CHILDREN (4-8 YEARS) | 2 mg |
| ADULTS/CHILDREN ( > 8 YEARS) | 3.3 mg |
| PREGNANT WOMEN | 3.3 mg |

### 4.6. Forms of Fluoride delivery

Fluoride is delivered through two main routes: systemic and topical. Systemic methods, such as community water fluoridation and dietary supplements like sodium fluoride tablets, fluoride-fortified milk and fluoridated salt. This route enhances enamel resistance to demineralization during tooth formation. Topical methods, including toothpaste, mouth rinses and professional gels or varnishes provide a direct application to the erupted tooth surface. Adding $F^-$ to the public water supply was considered one of the greatest successes in public health in the twentieth century and one of the most popular methods of delivering it systemically to a large population with no need for its active participation (21). In addition to community water fluoridation, fluoride supplements in the form of tablets and drops were originally introduced where fluoridated water was not available to provide optimal

exposure. Fluoride supplementation is currently very limited, reserved for consideration on an individual basis for high-risk patients (22).

Fluoride gels, for example, are available in concentrations ranging from 5,000 to 12,300 ppm. They are applied in disposable trays in the dental office to prevent caries and remineralize incipient lesions. They are contraindicated in children under 6 years of age due to the risk of ingestion with an unfavourable risk-benefit ratio. They can be applied to children over 6 years twice to 4 times per year, according to caries risk (22).

Another widely used topical option is fluoride varnish, a concentrated topical product (typically 22,600 ppm F) that is applied to the teeth and sets in contact with saliva. Since the risk of ingestion is extremely low it is also recommended for young children under 5 years. Among its advantages, it has a prolonged release and therapeutic effect and can be applied by both dental and nondental health professionals, especially in those children with limited access to dental care (22). Current guidelines recommend Fluoride varnish application for children at high risk of caries, every 3 to 6 months.

Moreover, silver diamine fluoride, available at a concentration of 44,800 ppm F, is a compound similar to a varnish that is applied on the tooth. Its antibacterial and remineralizing properties has proven highly effective both in preventing and arresting carious lesions in very young or uncooperative patients (22) .

### 4.7. Controversies and Ethical Considerations

Community water fluoridation remains a globally implemented public health strategy for dental caries prevention, supported by longitudinal evidence demonstrating caries reduction. Disability-adjusted life years (DALYs) analyses in Iran confirm fluoridation reduces caries burden, particularly benefiting children's dental health where water fluoride concentrations are suboptimal. However, socioeconomic factors significantly modify outcomes, as shown by the research where inequalities in dental caries persisted despite fluoridation when accounting for education and income (23,24). These disparities are consistent with observations in multiple European countries, where oral health outcomes have continued to improve despite limited or no water fluoridation. A multi-country assessment from seven European nations reported that widespread use of fluoride toothpaste and organized preventive dental programs were likely responsible for most

population-level improvements, suggesting that topical fluoride plays a greater role than systemic intake (25).

Additionally, the European analysis highlighted that most countries declined to implement water fluoridation due to ethical, cultural and social concerns about mass medication. Many health authorities in these nations concluded that the marginal benefit of systemic fluoride in water did not justify public opposition, especially when adequate oral health could be achieved through topical methods alone. This stands in contrast to countries such as the United States and Australia, where historical practices and different public health philosophies have maintained community water fluoridation programs (25).

One of the primary controversies focuses on the balance between beneficial effects and the risk of dental fluorosis is a dose-dependent condition resulting from excessive fluoride intake during tooth development, leading to aesthetic changes in enamel (ranging from mild white flecks to severe brown staining and pitting). While mild fluorosis is primarily a cosmetic issue, severe forms can impact self-esteem and oral health. Critics argue that achieving optimal caries prevention through water fluoridation inevitably exposes a segment of the population, particularly children, to levels of fluoride that may cause fluorosis. This raises ethical questions about individual autonomy and the potential for non-consensual medication, as individuals consuming fluoridated water may not have a choice in their fluoride exposure (26).

These ethical issues have resurfaced prominently in North America, where recent policy decisions have drawn attention to public concerns about mass exposure. In 2025, the Utah State ban on water fluoridation and subsequent national debate, including statements from the U.S. Health Secretary calling for an end to fluoridation illustrates growing scepticism toward compulsory public health interventions (27).

In response to increasing public pressure, the U.S. Environmental Protection Agency (EPA) announced a major review of new scientific evidence, particularly following a 2024 national toxicology program report suggesting that water fluoride levels > 1.5 mg $L^{-1}$ may be associated with lower IQ in children. This review signals a shift toward more cautious regulation and highlights the broader global debate on the necessity of systemic fluoridation in an era where topical fluoride is already widely available (27).

Another area of contention revolves around systemic health effects beyond dental fluorosis. Historically, studies have investigated the potential links between fluoride exposure and

various health outcomes, including bone health and neurodevelopmental effects. Regarding bone health, fluoride is known to accumulate in calcified tissues, constituting approximately 99% of the body's total fluoride content, largely through its incorporation into hydroxyapatite to form hydroxyfluoroapatite in bones and teeth (28). While moderate fluoride levels can strengthen bone, very high chronic exposure has been associated with skeletal fluorosis, a debilitating condition characterized by bone pain, stiffness, and increased fracture risk (28,29). Mathematical models have been developed to predict fluoride accumulation and clearance from the skeleton, considering factors like bioavailability and bone remodelling rate, highlighting the complex relationship between fluoride intake and skeletal effects. The distribution of fluoride in cortical bone of human ribs, for instance, has been shown to be highest in the periosteal region and decreases towards the endosteal surface, indicating a differential uptake within bone structures (30).

Recent large-scale toxicological evaluations provide further clarity on these risks. The 2025 EFSA Risk Assessment evaluation concluded that the most consistent adverse outcomes, including neurodevelopmental effects, thyroid alterations and changes to bone mineralisation are observed at total fluoride intakes corresponding to drinking water levels above 1.5 mg $L^{-1}$ (20). This threshold was identified across multiple lines of evidence, including human epidemiological studies and animal data.

Considering these findings, EFSA established new health-based guidance values to limit total fluoride exposure (Table 1). This included a safe intake level of 3.3 mg/day for pregnant women selected due to heightened fetal vulnerability to neurodevelopmental toxicity and substantially lower tolerable upper intake levels for infants and children (1.0–2.0 mg/day) based on dental fluorosis as the most sensitive endpoint. EFSA also noted that aggregate exposure from water, food, salt and ingested toothpaste can easily exceed these limits at the upper end of consumption, indicating that drinking water levels alone do not fully predict total fluoride burden (20).

Research consistently demonstrates biphasic effects, where low-dose fluoride prevents dental caries, but excessive intake causes dental/skeletal fluorosis. A recent review underscores this narrow therapeutic window, with fluorosis manifesting in populations exposed to groundwater fluoride >1.5 mg $L^{-1}$, while confirming caries reduction at 0.7-1.2 mg $L^{-1}$ (2). The methodological limitations in existing literature contribute to ongoing debates because much fluoridation evidence relies on population-level ecological studies,

complicating causal inferences about individual risk (31). Also, studies examining neurocognitive outcomes frequently struggle to disentangle fluoride effects from co-exposures (ex, lead or arsenic) and sociodemographic covariates (30,32,33).

Other works highlight more complex and sometimes concerning health implications. For example, a prospective Canadian birth cohort study (MIREC) reported that maternal fluoride exposure during pregnancy was associated with lower IQ scores in boys at age 3-4 years, with each 1 mg $L^{-1}$ increase in urinary fluoride corresponding to a 4.5 point decrease in IQ, on the other hand, no significant association was found in girls (32).

Furthermore, the "halo effect" of water fluoridation complicates the accurate assessment of fluoride exposure. This phenomenon refers to the widespread distribution of fluoride through processed foods and beverages made with fluoridated water, meaning individuals in non-fluoridated areas may still receive fluoride from their diet. This makes it challenging to accurately determine total fluoride intake and to conduct studies on populations with genuinely low fluoride exposure. The increased availability of fluoride from various sources, including fluoride-containing dental products and bottled water, further complicates the assessment of total body burden, moving beyond reliance solely on drinking water concentrations (26).

The development and assessment of new 18F-labeled tracers in positron emission tomography (PET) imaging also highlight the need for a comprehensive understanding of fluoride pharmacokinetics. Given that all 18F-labeled PET tracers are susceptible to defluorination and subsequent release of fluoride, particularly in experimental animals, it is crucial to assess the amount of released fluoride taken up by bones and other organs. Studies on rats have aimed to extensively document the pharmacokinetics of fluoride in bones and various organs, demonstrating its distribution to bones, blood, kidneys and lungs. These research efforts, while focused on imaging, underscore the intricate nature of fluoride's physiological handling and the need for careful consideration of its distribution and accumulation in biological systems (30).

Table 2 provides a comparative analysis of the primary literature surrounding fluoride usage. The data is categorized into two distinct scientific camps: those highlighting population-level efficacy and those raising significant concerns regarding individual developmental risks. This contrast illustrates the "pharmaceutical duality" where the benefits of a public health intervention must be weighed against emerging toxicological data.

*Table 2 - Papers in favor or against/ raising concerns on F- intake based on reported literature*

| Position | Article | Study Methodology | Key Results |
|---|---|---|---|
| In Favor | Water Fluoridation and Dental Caries in US Children and Adolescents (33) | **Cross-sectional analysis** of the most recent US National Health and Nutrition Examination Survey (NHANES) data. | Confirmed that exposure to optimally fluoridated water **significantly reduces caries prevalence** in the current US pediatric population. |
| | Water fluoridation for the prevention of dental caries (34) | **Systematic Review of 155 studies.** Comprehensive analysis of the effects of water fluoridation on tooth decay and fluorosis. | **Water fluoridation increases** the number of children with **no decay by 15% and decreases decayed,** missing, or filled teeth by 35%. Concluded it is an effective public health measure. |
| | Economic Evaluation of Community Water Fluoridation: A Community Guide Systematic Review (35) | **Systematic Review & Economic Evaluation.** Analyzed the cost-benefit and cost-effectiveness of water fluoridation programs. | Concluded that **water fluoridation is cost-saving**. The return on investment is especially high for larger communities, saving money for both the healthcare system and families. |
| | Does cessation of community water fluoridation lead to an increase in tooth decay? A systematic review of published studies (36) | **Systematic Review**. Analyzed studies that examined what happened to dental health in communities that stopped water fluoridation. | Found that the **cessation of water fluoridation was associated with an increase in dental caries** in children. Provided indirect, strong evidence that fluoridation is effective. |
| | A cost-effectiveness analysis of community water fluoridation for schoolchildren (37) | **Economic Evaluation**. Analyzed the cost-benefit of water fluoridation | Found that water fluoridation is a **cost-saving public health intervention**, providing significant economic benefits by reducing treatment costs. |
| | | | |
| Against or Raising Concerns | Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 Years of Age in Mexico (38) | **Prospective Birth Cohort Study.** Measured maternal urinary fluoride and assessed child cognitive performance over time. | A 0.5 mg $L^{-1}$ increase in maternal urinary fluoride was associated with a **2.5-point lower IQ score** in children at 6-12 years. This was a dose-dependent relationship. |
| | A Benchmark Dose Analysis for Maternal Pregnancy Urine-Fluoride and IQ in Children (39) | **Birth Cohort Analysis & Benchmark Dose Modelling.** This study re-analyzed data from the Bashash (2017) and Green (2019) cohorts using a specific statistical model to determine a "safe" level of exposure | **Fluoride exposure at the level recommended for water fluoridation (0.7 ppm) was associated with a decrease in child IQ.** The calculated Benchmark Dose (BMDL) for a 1-point IQ loss was lower than the exposure levels in fluoridated communities. |
| | Effect of Endemic Fluorosis on Cognitive Function of School Children in Alappuzha District, Kerala: A Cross-Sectional Study (40) | **Cross-Sectional Study.** Examined fluoride exposure, dental fluorosis, and cognitive performance in a Canadian population. | Higher fluoride exposure was associated with a **higher prevalence of dental fluorosis** and, separately, with **lower performance on cognitive tests** assessing memory and fluid intelligence. |
| | Critical windows of fluoride neurotoxicity in Canadian children (41) | **Birth cohort analysis** to identify sensitive exposure period | Identified the **second and third trimesters of pregnancy** as critical windows for fluoride's negative impact on child IQ. |

The synthesis of these studies reveals a division in the evidence, while systematic reviews from established public health bodies confirm the cost-effectiveness and success of water fluoridation, recent birth cohort studies demonstrate a statistically significant correlation between prenatal fluoride exposure and cognitive decline. This divergence in the research suggests that the historical 'one-size-fits-all' approach to systemic fluoridation is no longer supported by a total consensus, justifying a shift toward more cautious individualized topical treatments.

## 5. Impact of Fluoride on the Oral and Intestinal Microbiome

The human microbiome plays a critical role in maintaining homeostasis and emerging pharmaceutical research has begun to explore how fluoride exposure, both topical and systemic, influences these complex microbial communities. The interaction between fluoride and the microbiome is characterized by a "selective pressure" mechanism where different microbial species exhibit varying levels of sensitivity or resistance to the fluoride ion (42).

### 5.1. The Oral Microbiome: Selective Antimicrobial Action

In the oral cavity, fluoride acts not only by strengthening enamel but also by functioning as a selective antimicrobial agent. Recent research indicates that stannous-containing sodium fluoride ($SnF_2$) dentifrices provide a superior benefit in maintaining oral balance compared to conventional formulations (43). Stannous ions ($Sn^{2+}$) have been shown to preferentially target and co-localize with periodontal pathogens, such as *Porphyromonas gingivalis*, effectively reversing dysbiosis without significantly disrupting health-associated commensal species (43). Furthermore, a critical molecular distinction exists in how oral bacteria handle fluoride toxicity. Health-associated streptococci utilize highly efficient fluoride channels to export the ion, giving them a competitive fitness advantage in dental biofilms over pathogenic species like *Streptococcus mutans*, which rely on less efficient $F^-/H^+$ antiporters (44). This selective inhibition helps maintain a neutral pH environment, preventing the overgrowth of acidogenic bacteria (44).

### 5.2. The Intestinal Microbiome: Systemic Effects and Dysbiosis

While the topical benefits in the mouth are well-documented, the impact of ingested (systemic) fluoride on the gut microbiota is a subject of growing concern. A 2025 systematic review of studies concluded that fluoride behaves as a dose-dependent modulator of the intestinal environment (45). In humans, low concentrations (≤2 mg $L^{-1}$) appear to have harmless or even positive effects on microbial composition however high systemic doses can significantly disrupt the Firmicutes-to-Bacteroidetes ratio (biomarker frequently cited in the scientific literature as a hallmark of obesity) leading to microbial dysbiosis (45).

Excessive fluoride intake has been linked to an increased relative abundance of Proteobacteria and Acidobacteria, which are often associated with inflammatory states, while simultaneously decreasing the abundance of beneficial taxa like *Bifidobacterium* (45). These changes can impair the gut barrier function and trigger metabolic disruptions, highlighting a potential link between high fluoride exposure and systemic gastrointestinal health issues (45).

## 6. World Health Organization (WHO) Global Strategy and Objectives

The WHO has recently updated its global agenda through the Global Strategy and Action Plan on Oral Health 2023-2030, which establishes a definitive path toward Universal Health Coverage for oral health by the end of the decade (46).

This strategic framework seeks to ensure that 80% of the global population is entitled to essential oral health care services and aims for a 10% relative reduction in the global prevalence of major oral diseases and conditions over the life course (46). A central component of this plan is the commitment to optimal fluoride delivery, specifically, the WHO aims for 50% of member states to implement national guidance on the effective and safe use of fluoride for their populations by 2030 (46).

Furthermore, the strategy highlights the importance of oral health promotion and disease prevention by making essential dental products, such as fluoride toothpaste, both accessible and affordable for all communities (46).

These objectives are integrated into a broader public health approach that reorients traditional curative dentistry toward a preventive model, while also encouraging countries

to strengthen their surveillance systems to map and track fluoride concentrations in drinking water to balance protective efficacy against the risk of fluorosis (46).

## 7. Conclusion

The critical analysis presented in this dissertation demonstrates that fluoride is a pharmacological agent of undeniable importance characterized by a narrow therapeutic window where the boundary between therapeutic benefit and systemic toxicity is strictly defined by precise dosing. Although the formation of acid-resistant fluorapatite and the inhibition of demineralization have been pillars of public health success in the 20th century, the contemporary global landscape reveals a scenario of increasing scientific and ethical complexity. The phenomenon known as the "halo effect", the uncontrolled ingestion of fluoride through processed foods and beverages produced in fluoridated areas, complicates the regulation of total fluoride body burden and raises questions about the necessity of systemic water fluoridation in populations that already have access to multiple sources. This divergence in the research suggests that the historical "one-size-fits-all" approach to systemic fluoridation is no longer supported by a total consensus of evidence, justifying a shift toward more cautious and individualized topical treatments.

Recent evidence from risk assessments by the EFSA and the U.S. National Toxicology Program in 2024 and 2025 has identified significant concerns regarding neurocognitive risks, including a reduction in intelligence quotient in children exposed to fluoride levels exceeding 1.5 mg $L^{-1}$. Furthermore, exploring the impact of fluoride on the microbiome reveals that while topical application, especially with stannous ions, helps maintain oral homeostasis and prevent dysbiosis, excessive ingestion can act as a dose-dependent modulator in the intestinal environment, potentially leading to alterations in the microbiota and intestinal barrier function. These findings align with the WHO Global Strategy and Action Plan on Oral Health 2023-2030, which aims to ensure that 80% of the world's population will have access to essential oral health services and that 50% of Member States implement national guidelines for the safe and optimal delivery of fluoride by 2030. This plan emphasizes the need to reorient curative dentistry toward a preventive model, integrating the monitoring of fluoride levels in drinking water to balance protective efficacy with the prevention of endemic fluorosis.

Future perspectives for the pharmaceutical and public health sectors must focus on developing aggregate exposure models that accurately quantify total fluoride body burden. It is imperative to invest in research on long-term exposure biomarkers to allow for the early detection of potential adverse effects before clinical symptoms manifest. Furthermore, public policies should evolve toward risk-stratified health strategies, reserving systemic supplementation for high-risk individuals and prioritizing topical delivery methods such as varnishes and toothpastes for the general population. This approach maximizes dental protection while minimizing the risks of systemic toxicity and iatrogenic harm, ensuring that fluoride remains a safe and effective tool in modern healthcare.

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