The Impact Of Sodium Fluoride On Biological Systems, Organs, Tissues, Cells and Sub-cellular Components: A Comprehensive Scientific Review

Abofila MTM
Department of Histology & Genetics, Faculty of Medicine, Sabratha University, Libya
marwan.abofila@sabu.edu.ly

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Abstract
Background: Sodium fluoride is a widely utilized compound in industrial processes and oral health products, impacting biological systems across multiple hierarchical levels, including organs, tissues, cells, and subcellular structures. While its dental benefits are well established, chronic or excessive exposure disrupts enzymatic activity and function, impairs mitochondrial integrity, and perturbs redox balance, leading to apoptosis, inducing autophagy, and activating inflammatory responses. Understanding these mechanisms is critical for accurate toxicological assessment and for the development of safe, evidence-based applications. **Objectives:** This review critically evaluates sodium fluoride's impact across multiple biological levels, from subcellular components to tissues and organs, integrating experimental, clinical, and toxicological evidence. It delineates its chemical properties, exposure pathways, and pharmacokinetics—including absorption, distribution, metabolism, and excretion—while highlighting molecular and cellular mechanisms underlying systemic effects. Dose–response dynamics, exposure duration, and cumulative risk frameworks are examined to distinguish therapeutic benefits from potential toxicity. The review addresses ongoing controversies, methodological limitations, and variability in findings, while discussing protective strategies, public health policies, and ethical and environmental considerations. By synthesizing multidisciplinary evidence, it provides a balanced foundation for safe fluoride use and future research priorities. **Conclusion:** This review synthesizes current evidence on sodium fluoride's effects across molecular, cellular, tissue, organ, and systemic levels. Its biological impact is mediated via complex mechanisms, including enzyme modulation, oxidative stress, mitochondrial function, ion transport, and signaling cascades, with outcomes influenced by concentration, exposure duration, and developmental context. Systemic effects involve calcified tissues, endocrine organs, renal systems, and neural structures, with heightened vulnerability during prenatal and early postnatal stages. Risk assessment requires integration of dose–response data, exposure dynamics, and population variability. Evidence-based mitigation, ethical regulation, and interdisciplinary research are essential to optimize therapeutic benefits while minimizing biological and environmental risks.

Keywords: *Sodium Fluoride, Chemical Nature, Exposure Pathways, Mechanisms of Action, Biological Systems impact, Organs, Tissues, Cells, Sub-cellular Components, Developmental Considerations, Absorption, Distribution, Neurobiological Processes, Endocrine Interactions, Metabolic Effects, Dose, Duration, Risk Assessment, Protective, Mitigating Strategies, Public Health Policy Implications, Ethical Considerations, Environmental Perspectives*

1. Introduction:

Fluoride is a naturally occurring element present in human habitats, commonly as sodium fluoride (NaF) in both solid and aqueous forms. Sodium fluoride plays a crucial role in industrial processes, including the production of glass, ceramics, and aluminum, and serves as a flux in metallurgy. It is also an important precursor for synthesizing organofluorine compounds (Kamruzzaman *et al.,* 2025; Olejarczyk *et al.,* 2022). Despite its industrial significance, sodium fluoride has been widely incorporated into oral hygiene products, such as toothpaste and mouthwash, due to its well-established efficacy in preventing dental caries. However, its strong biological activity classifies its use as a potentially hazardous substance under United Nations guidelines (Almishkhas *et al.,* 2025; Talebi et al., 2025; Guth *et al.,* 2020).

The biological effects of fluoride have been recognized for over sixty years, with concerns regarding excessive or unintended exposure increasingly documented (Sotili *et al.,* 2025; Lubojanski *et al.,* 2023). Fluoride can form solvated complexes that modulate enzymatic activity, act as a second messenger in intracellular signaling, influence cell proliferation, and disrupt hepatic glucose metabolism (Li, 2003). Experimental studies have demonstrated its ability to induce hepatocyte proliferation following partial hepatectomy and stimulate neurogenesis in cultured brain slices (Du *et al.,* 2024). These findings illustrate the multifaceted biological impact of fluoride and underscore the need for careful assessment of exposure levels (Chavarria, 2025; Chhabra *et al.,* 2025).

Sodium fluoride has also been shown to accumulate in reproductive organs, interfering with hormonal regulation and oxidative stress pathways, contributing to reproductive toxicity (Chhabra *et al.,* 2025; Talebi *et al.,* 2025). Beyond reproductive effects, chronic exposure impacts hepatic, renal, neuronal, and skeletal tissues, as well as subcellular structures such as mitochondria (Talebi *et al.,* 2025; Lima *et al.,* 2021). Mechanistically, fluoride inhibits Na^+/K^+-ATPases, depletes ATP, disrupts mitochondrial membrane potential, and induces apoptosis via cytochrome-c release (Talebi *et al.,* 2025; Avila-Rojas *et al.,* 2022).

These effects are compounded by autophagic activation and inflammatory responses, amplifying cellular damage across multiple organ systems (Chhabra *et al.,* 2025; Talebi *et al.,* 2025). Additionally, fluoride promotes intracellular calcium complex formation, disrupting the electron transport chain and redox balance, generating reactive oxygen species that trigger apoptotic cell death (Kumar *et al.,* 2024; Wei *et al.,* 2022; Angwa *et al.,* 2021). Genetic susceptibility further modulates these toxicological responses, highlighting the complexity of fluoride's systemic impact (Chhabra *et al.,* 2025; Talebi *et al.,* 2025; Wu *et al.,* 2022).

The significance of this article lies in its rigorous and multidisciplinary integration of contemporary scientific literature on the biological effects of sodium fluoride, encompassing multiple hierarchical levels of biological organization, from molecular and subcellular processes to whole organ and systemic physiological functions. In addition, in light of recent research, it observes its chemical properties and exposure pathways, clarifying how environmental, dietary, and industrial sources influence human health. It also elucidates its mechanisms of action within biological systems. Furthermore, it emphasizes developmental and neurobiological susceptibility, pharmacokinetics, endocrine interactions, and metabolic effects, while providing a critical evaluation of dose response relationships, exposure duration, and risk assessment frameworks to distinguish therapeutic benefits from potential toxicity. By addressing scientific controversies, reviewing methodological approaches, examining protective and mitigating strategies, and discussing public health policies as well as ethical and environmental considerations, the review promotes a balanced, evidence based understanding of sodium fluoride. Ultimately, it highlights research gaps and future priorities, thereby supporting informed clinical practice, regulatory decision making, and sustainable public health strategies.

2. Objectives:

This comprehensive scientific review aims to provide a rigorous, integrative, and multidisciplinary evaluation of the impact of sodium fluoride on biological systems at multiple levels of organization, including organs, tissues, cells, and sub-cellular components. The article seeks to synthesize current experimental, clinical, epidemiological, and toxicological evidence to clarify how sodium fluoride interacts with living systems under varying exposure conditions. Particular attention is given to its chemical characteristics and major exposure pathways, including environmental, dietary, occupational, and public health sources, in order to contextualize systemic biological effects within real-world exposure scenarios. The review further aims to elucidate the molecular and cellular mechanisms underlying fluoride activity, including its influence on enzymatic processes, oxidative stress pathways, mitochondrial function, membrane integrity, DNA stability, and intracellular signaling networks. In doing so, it examines how these mechanistic alterations translate into functional and structural changes at the tissue and organ levels, with emphasis on skeletal, dental, renal, hepatic, endocrine, and neurobiological systems. Developmental and neurophysiological considerations are also explored to assess potential vulnerabilities during critical life stages, particularly prenatal and early childhood periods.

In addition, this article evaluates the pharmacokinetic profile of sodium fluoride its absorption, distribution, metabolism, and excretion alongside its endocrine interactions and broader metabolic consequences. A central objective is to critically analyze dose-response relationships, exposure duration, and cumulative risk assessment models in order to distinguish beneficial therapeutic thresholds from potentially harmful levels. The review also addresses ongoing scientific controversies and debates in fluoride biology, highlighting methodological challenges, inconsistencies in findings, and areas requiring further clarification. Moreover, the article aims to assess current methodological approaches used in fluoride research, including in vitro systems, animal models, biomonitoring strategies, and large scale epidemiological investigations. It considers protective and mitigating strategies designed to reduce adverse biological effects while preserving recognized public health benefits. Finally, the review examines the broader implications for public health policy, ethical accountability, and environmental sustainability, and identifies priority areas for future research. Through this comprehensive framework, the article intends to support evidence based decision making and promote a balanced understanding of sodium fluoride's biological impact across levels of biological complexity.

2. Chemical Nature and Exposure Pathways of Sodium Fluoride:

Sodium fluoride (NaF) is a white crystalline powder that exists as a solid in nature, naturally occurring in minerals, and in fortified products. It is hygroscopic and forms aqueous solutions containing fluoride ions (F^-). The pH of an NaF solution varies with concentration from 4.5 (5% solution) to 8.8 (0.1% solution), and the corresponding free ion concentrations increase or decrease according to the pH, specifications determined for other fluorides are similar. NaF is produced by neutralizing fluorosilicic acid with dry caustic soda and is widely transported as solid or aqueous solutions, often in combination with sodium hexafluorsilicate (Lubojanski *et al.*, 2023; Guth *et al.*, 2020).

Globally, drinking-water fluoridation programs are among the most costly public health initiatives undertaken by local and national governments. (Sexton *et al.*, 2026; Yeh *et al.*, 2025). In contrast, assessments conducted by the United States Environmental Protection Agency (EPA) and regulatory authorities within the European Union (EU) have reported no demonstrable health benefits associated with fluoride concentrations above zero, thereby supporting calls for the prompt and voluntary discontinuation of water fluoridation practices (Sexton *et al.*, 2026; Choi & Simon, 2025).

3. Mechanisms of Action in Biological Systems:

Cate (1999) explained that the sodium fluoride affects biological systems through several well-characterized biochemical and cellular mechanisms. Its effects depend strongly on dose, duration of exposure, and tissue type. The dose-dependent profile, outlining the exposure levels and their principal biological effects, is presented in Table (1). Its effects within biological systems are mediated through the following mechanisms:

1) **Effects on Teeth (Anti-Caries Action):**
   a) **Formation of Fluorapatite:** Fluoride ions (F^-) replace hydroxyl groups (OH^-) in hydroxyapatite crystals of enamel:
      - Hydroxyapatite → Fluorapatite.
      - Fluorapatite is:
        - More resistant to acid dissolution.
        - Less soluble at low pH.
        - More stable against bacterial acid attack.

      This increases enamel hardness and reduces dental caries (Ambarkova, 2025; Honóriob & ten Cated, 2011).
   b) **Remineralization Enhancement:** Al-Shaibani *et al.* (2025) confirmed that the roles of fluoride include the following:
      - Promotes deposition of calcium and phosphate ions.
      - Enhances remineralization of early enamel lesions.
      - Inhibits demineralization during acid exposure.
   c) **Antibacterial Effects:** Both research groups, Bhat *et al.* (2024) and Thurnheer and Belibasakis (2018), reported that fluoride is involved in the following biological processes.
      - Inhibits bacterial enzyme enolase (glycolytic pathway).
      - Reduces acid production by cariogenic bacteria (e.g., Streptococcus mutans).
      - Disrupts proton gradients in bacterial membranes (as HF diffusion).
      - Result: Reduced plaque acidity and caries formation.
2) **Effects on Biological Enzymes:** Strunecka & Strunecky (2020) emphasized that fluoride forms complexes (e.g., AlF_4^-, BeF_3^-) that mimic phosphate groups and lead to:
   a) **Inhibition of Enzymes Activities / Metabolic:**
      - Inhibits enolase (glycolysis).
      - Inhibits phosphatases.
      - Alters ATPase activity.

      The effect initiate:
      - Decreased ATP production.
      - Altered cellular metabolism.
   b) **G-Protein Activation Mimicry:** Fluoride–aluminum complexes (AlF_4^-):
      - Mimic the γ-phosphate of GTP.
      - Stabilize G-proteins in active conformation.
      - Activate downstream signaling pathways.

      This is widely used experimentally to study signal transduction.
3) **Effects on Bone:** Kanduti *et al.* (2016) highlighted the following effects:
   a) **Osteoblast Stimulation (Low to Moderate Doses):**
      - Increases bone formation.

- Stimulates osteoblast proliferation.
- Historically used in osteoporosis therapy (now largely discontinued).

b) **Skeletal Fluorosis (High/Chronic Exposure):** Excess fluoride lead to:

- Alters bone mineralization.
- Causes increased bone density but reduced quality.

The effect leads to:

- Joint stiffness.
- Bone deformities.
- Calcification of ligaments.

4) **Cellular and Molecular Toxicity (High Doses):** Johnston & Strobel (2020) demonstrated that high concentrations of fluoride exert cytotoxic effects through multiple cellular and molecular mechanisms:

a) **Oxidative Stress:** High fluoride levels that cause:

- Increase reactive oxygen species (ROS).
- Reduce antioxidant enzyme activity.
- Cause lipid per-oxidation.

b) **Mitochondrial Dysfunction:**

- Reduces ATP production.
- Inhibits mitochondrial enzymes.
- Induces apoptosis (programmed cell death).

c) **Endocrine Effects:** High exposure may:

- Affect thyroid function.
- Interfere with iodine uptake (at excessive levels).

Table (1): Dose-Dependent Effects of Fluoride Exposure: Cate (1999) described the dose-dependent biological effects of fluoride as follows::

Dose Level	Primary Effect
Low (topical)	Anti-caries, enamel strengthening
Moderate (systemic)	Bone stimulation
High (chronic)	Skeletal fluorosis
Very high (acute)	Enzyme inhibition, hypocalcemia & metabolic toxicity

Fluoride exerts its biological effects through multiple, well-characterized mechanisms. Principally, it substitutes for hydroxyl groups within mineralized tissues, thereby altering crystal structure and physicochemical properties. At the molecular level, fluoride can mimic phosphate in enzymatic reactions, influencing phosphorylation-dependent processes (Piszko *et al.*, 2024). It also inhibits several key metabolic enzymes, contributing to disruptions in cellular metabolism. In addition, fluoride modulates intracellular signaling pathways, potentially affecting gene expression and regulatory networks. At elevated or toxic concentrations, these mechanisms are further compounded by the induction of oxidative stress, leading to cellular dysfunction and tissue injury (Pal *et al.*, 2023).

Generally, biochemical pathways affected by sodium fluoride encompass cell signaling and gene regulation, with cellular and subcellular levels activated or inhibited by different concentrations (Patel *et al.*, 2024; Nagendra *et al.*, 2021). At low fluoride concentrations, cell signaling factors such as ERK, CREB, and SIRT1 are stimulated, along with genes protective against oxidative stress (Gu *et al.*, 2026; Atri *et al.*, 2025; Ferreira *et al.*, 2025; Xie *et al.*, 2025). Tissue injury and proapoptotic factors are induced at moderate fluoride levels, while high concentrations cause severe organ damage and mitochondrial dysfunction (Ferreira *et al.,* 2025; Kumar *et al.,* 2024; Zhu & Wei, 2024). Fluoride activates destruction of the cytoskeleton and cytoplasmic organelles, together with apoptosis proteases, at its upper-effective concentration. Direct exposure to NaF initiates intracellular signaling related to actin cytoskeleton remodeling and shape alteration (Ferreira *et al.,* 2025; Zhang et al., 2025; Wu *et al.,* 2022). Fluoride exposure entails risky bioaccumulation and signal transduction modulation, leading to systemic fluoride distribution variations (Ferreira *et al.,* 2025; Wang *et al.,* 2023).

4. Effects on Cells and Subcellular Components:

Sodium fluoride exerts profound effects on cellular and subcellular structures, disrupting processes essential for cell viability, proliferation, and homeostasis, as well as markedly inhibiting cell growth at high concentrations (Johnston & Strobel, 2020). At the plasma membrane, fluoride compromises lipid bilayer integrity and modulates ion channel activity, thereby altering membrane permeability in cultured neurons and astrocytes. These alterations are associated with increased lactate depletion and impaired cellular signaling and transport (Bhat, 2025; Singh *et al.,* 2025; Chauhan & Kumar, 2025; Puty *et al.,* 2021).

Moreover, within the cytoplasm, fluoride perturbs enzyme kinetics, metabolic pathways, and redox homeostasis by increasing reactive oxygen species (ROS) generation and inhibiting antioxidant defenses (Zeng *et al.,* 2025). Mitochondria are particularly sensitive, exhibiting membrane depolarization and loss of membrane potential in bone marrow–derived mesenchymal stem cells, as well as ATP depletion, electron transport chain dysfunction, mitochondrial swelling, and intracellular calcium elevation. These alterations enhance reactive oxygen species production and disrupt cytoskeletal organization, thereby activating intrinsic apoptotic pathways, inducing the caspase cascade, and promoting autophagic processes as adaptive responses to fluoride exposure in various cell types (Kumar *et al.,* 2024; Kuang *et al.,* 2022).

Nuclear and nucleolar functions are also affected, with fluoride destabilizing nucleic acids, altering chromatin architecture, and triggering DNA damage responses. Notably, simultaneous calcium chelation markedly attenuates γ-H2AX and 53BP1 nuclear foci formation, as well as the upregulation of p53 and p21 expression (Puty *et al.,* 2021). Cytoskeletal organization is disrupted, lysosomal exocytosis is enhanced, and cell proliferation is substantially inhibited at high fluoride concentrations. These effects have been observed across diverse cell types, including neurons, astrocytes, splenic lymphocytes, and bone marrow derived mesenchymal stem cells, impacting multiple organ systems both in vitro and in vivo during development and adulthood (Kuang *et al.,* 2022; Puty *et al.,* 2021).

Collectively, these findings demonstrate that sodium fluoride compromises cellular integrity and function through coordinated disturbances of mitochondrial, nuclear, and cytoplasmic processes. The severity of toxicity depends on concentration, exposure duration, and cellular context, underscoring the importance of mechanistic investigations to inform accurate toxicological assessment, therapeutic evaluation, and the development of protective strategies in biological systems (Liu *et al.,* 2025).

5. Tissues and Organs: Systemic Impacts:

Systemic effects of sodium fluoride primarily arise from ingestion and, to a lesser extent, inhalation. Once absorbed, the compound circulates via blood serum and tissue fluid and is distributed to various organs, and exerts multi-organ systemic effects that reflect its bioavailability, tissue affinity, and cumulative exposure dynamics (Dumpala *et al.,* 2025; Lopes *et al.,* 2020). Notably, those with calcifying tissues and properties, particularly bone and dental structures, serve as primary reservoirs due to fluoride's strong affinity for hydroxyapatite crystals (Narvai *et al.,* 2026; Sedek& Holiel, 2025). At physiologically regulated concentrations, fluoride enhances enamel resistance and modulates bone mineralization; however, excessive or prolonged exposure disrupts skeletal remodeling, alters mineral density, and may culminate in structural and functional impairments characteristic of fluorosis (Uğuz *et al.,* 2026).

In soft tissues, fluoride distribution influences hepatic, renal, endocrine, and neural systems. Hepatic exposure is associated with altered glucose metabolism, enzyme dysregulation, and oxidative stress induction, while renal tissues central to fluoride clearance may exhibit tubular dysfunction and compromised filtration under chronic burden (Meenakshi *et al.,* 2025; Lavanya *et al.,* 2024; Sharma *et al.,* 2023). Endocrine perturbations include interference with thyroid homeostasis and reproductive hormonal signaling, thereby affecting systemic metabolic regulation (Stencel *et al.,* 2026; Zeng *et al.,* 2021). In the central nervous system, fluoride exposure has been linked to mitochondrial dysfunction, redox imbalance, neuroinflammatory activation, and altered synaptic signaling, raising particular concern for developmental susceptibility (Bhat *et al.,* 2024; Ghosh & Ghosh, 2020).

According to the available evidence, systemic fluoride concentrations that are deleterious to tissues beyond bone and teeth fall within the range observed in human populations exposed to fluoridated water. Collectively, these findings indicate that sodium fluoride exerts effects beyond localized dental tissues, influencing integrated physiological systems (Kabir *et al.,* 2020). Organ-specific vulnerability is modulated by dose, exposure duration, developmental stage, and genetic susceptibility. Consequently, sodium fluoride specific insights into the repercussions of chronic exposure provide valuable information regarding the system-wide impacts of free fluoride ions. A mechanistic understanding of tissue level responses is therefore essential to refine risk assessment models and to ensure that public health applications maximize therapeutic benefit while minimizing systemic toxicity (Pal *et al.,* 2023).

6. Developmental and Neurobiological Processes:

Sodium fluoride exposure during critical periods of development exerts significant neurobiological effects. Evidence indicates that both prenatal and early postnatal exposure can disrupt neurogenesis, synaptogenesis, and neuronal migration, ultimately affecting brain structure and function. Furthermore, developmental toxicity has been observed in rodents, neurodevelopmental outcomes have been associated with maternal seafood consumption, and altered expression of G proteins has been reported in embryonic neurons (Guth *et al.,* 2020).

These effects are mediated through alterations in oxidative stress balance, mitochondrial function damage, calcium signaling, and neurotransmitter systems. (Adkins & Brunst, 2021). Studies have investigated fluoride's impact on intelligence in children, finding correlations with dental fluorosis and IQ (Taylor *et al.,* 2025). Some research, particularly from areas with high natural fluoride levels in drinking water, has reported an association between elevated fluoride exposure and slightly lower IQ scores (Xia *et al.,* 2024). In certain cases, children who showed signs of moderate to severe dental fluorosis, a condition caused by excessive fluoride intake during tooth development were also found to have lower average intelligence scores compared to children with minimal or no fluorosis (Cross, 2025; de Oliveira *et al.,* 2025).

However, most of these studies identify correlations rather than direct causation. Factors such as socioeconomic status, nutrition, exposure to other environmental toxins, parental education, and overall health can also influence cognitive development. Major health organizations like the World Health Organization and the Centers for Disease Control and Prevention maintain that controlled water fluoridation at recommended levels is safe and effective for preventing dental caries (Chamarthi *et al.,* 2025). On the whole, while some evidence suggests a possible link between high fluoride exposure and reduced

IQ, especially in areas with excessive fluoride levels, further well-controlled research is needed to clarify the relationship and determine safe exposure thresholds (Taylor *et al.*, 2025; Yu *et al.*, 2018).

7. Absorption, Endocrine Interactions and Metabolic Effect:

Researchers have investigated the potential effects of sodium fluoride on physiological processes, including its absorption, distribution, endocrine interactions, and metabolic functions within the body particularly at elevated exposure levels (Zhou *et al.,* 2023). These investigations have identified several possible biological impacts, as outlined beneath:

- **Absorption and Distribution:**
  Ranjan & Ranjan (2015) exposed that the fate of sodium fluoride after ingestion is as follows:
  - Is rapidly absorbed in the stomach and small intestine.
  - Circulates in plasma, where it can cross cell membranes.
  - Accumulates primarily in bones and teeth.
  - Can cross the blood-brain barrier and placenta (at measurable levels).

  The degree of systemic effect depends on dose, duration of exposure, kidney function, age, and nutritional status.
- **Effects on the Endocrine System:**

A. Thyroid Function:

The thyroid gland is one of the most studied endocrine targets.

Mechanism:
- Fluoride can compete with iodine uptake in the thyroid.
- It may inhibit enzymes involved in thyroid hormone synthesis.
- At high levels, it may interfere with T3 and T4 production.

Observed effects (mainly in high-exposure areas):
- Reduced T3/T4 levels.
- Altered TSH (thyroid-stimulating hormone).
- Increased risk of hypothyroid-like patterns in iodine-deficient populations.

However, at fluoridation levels used in most public water systems ($\approx$0.7 mg/L), evidence of clinically significant thyroid disruption in iodine-sufficient populations remains inconsistent (Dhurvey *et al.*, 2017).

B. Parathyroid and Calcium Regulation:

Wang *et al.* (2015) illustrated that fluoride has strong interactions with calcium and bone metabolism.

Mechanism:
- Stimulates osteoblast activity (bone-forming cells).
- Alters bone remodeling.
- May increase parathyroid hormone (PTH) in some high-exposure settings.

Observed effects (chronic high intake can contribute to skeletal fluorosis) that characterized by:
- Increased bone density.
- Joint stiffness.
- Altered mineral metabolism.

C. Insulin Function and Glucose Regulation:

Animal studies suggest:

Mechanism:
- High doses may impair insulin secretion.
- May induce oxidative stress in pancreatic β-cells.
- Possible alterations in glucose tolerance.

Observed effects: Sodium fluoride has been studied for its potential effects on the insulin function and glucose metabolism, particularly in cases of chronic exposure or high intake that characterized by:

- **Effects on Insulin Function:**
  - **Altered insulin Secretion levels:** Animal studies have shown both decreased and, in some cases, compensatory increased insulin levels following fluoride exposure, depending on dose and duration.
  - **Impaired insulin signaling:** Some evidence suggests that fluoride may interfere with insulin receptor signaling pathways, which could affect glucose uptake by tissues.
- **Effects on Glucose Regulation**
  - **Changes in blood glucose levels:** High levels of fluoride exposure in animal models have been linked to elevated blood glucose levels (hyperglycemia).
  - **Insulin resistance:** Chronic exposure has been associated in some studies with reduced insulin sensitivity.
  - **Dose dependency:** These metabolic effects are generally observed at high fluoride concentrations and may not occur at levels typically used in community water fluoridation.

Human evidence is limited and mixed. Most evidence for fluoride's effects on the pancreas and glucose metabolism comes from animal studies using relatively higher than typical environmental exposures. At recommended levels for dental health (such as in fluoridated water), current research does not consistently demonstrate significant adverse effects on insulin secretion or glucose regulation in humans. Further well controlled human studies are needed to clarify long-term metabolic impacts (Lombarte *et al.,* 2016; Chiba *et al.,* 2012).

D. Reproductive Hormones Function:

Preceding study (primarily animal or high-exposure human populations) by Tang *et al.* (2018) revealed that:

Mechanism:

- Altered testosterone levels.
- Changes in estrogen balance.
- Potential effects on sperm morphology and ovarian function.

Observed effects: The effects of sodium fluoride on reproductive hormones have been investigated mainly in animal studies and in populations exposed to high levels of fluoride. Findings vary depending on dose, duration of exposure, age, and sex, which include the following:

- **Effects on Male Reproductive Hormones:** Al-Sabaawy& Al-Kaisie (2020) showed that:
  a) Testosterone:
    - **Reduced testosterone levels:** Several animal studies have reported decreased serum testosterone following chronic high-dose fluoride exposure.
    - **Leydig cell alterations:** Structural and functional changes in Leydig cells (which produce testosterone) have been observed in experimental models.
    - **Oxidative stress:** Increased oxidative stress in testicular tissue may impair steroid hormone synthesis.

b) Gonadotropins (LH and FSH):
- Some studies have reported altered levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), possibly reflecting disruption of the hypothalamic pituitary gonadal (HPG) axis.
- Results are inconsistent, with both increases and decreases reported depending on exposure conditions.

- **Effects on Female Reproductive Hormones:** Fishta *et al.* (2025) explained that:

a) Estrogen and Progesterone:
- Animal studies suggest that high fluoride exposure may reduce circulating estrogen and progesterone levels.
- Structural changes in ovarian tissue, including follicular degeneration, have been described in experimental settings.

b) Ovarian Function
- Alterations in estrous cycles have been reported in rodents exposed to elevated fluoride concentrations.
- Possible disruption of follicular development and ovulation has been observed at high doses.

- **Effects on the Hypothalamic Pituitary Gonadal (HPG) Axis:** Santos *et al.* (2025) elucidated that:
  - Fluoride may influence hormone regulation at multiple levels of the HPG axis.
  - Some studies suggest altered secretion of gonadotropin-releasing hormone (GnRH), LH, and FSH.
  - These effects are generally linked to high or prolonged exposure and may involve oxidative stress and endocrine disruption mechanisms.
- **Human Evidence:**
  - In regions with endemic fluorosis (high environmental fluoride exposure), some studies have reported associations with altered reproductive hormone levels.
  - However, findings in humans are inconsistent and often confounded by nutritional status, environmental factors, and overall health conditions.
  - At fluoride levels typically used in community water fluoridation, current evidence does not consistently demonstrate clinically significant effects on reproductive hormone function.

Most reported effects of sodium fluoride on reproductive hormones are derived from animal studies using relatively high doses. Observed changes include alterations in testosterone, estrogen, progesterone, LH, and FSH levels, as well as structural changes in reproductive tissues. The relevance of these findings to typical human exposure levels remains uncertain, and more well-designed human studies are needed to clarify (Talebi *et al.,* 2025; Skórka-Majewicz *et al.*, 2020).

- **Metabolic Effects:**

A. Enzyme Activity:

Both Choudhary & Bohra (1989) exhibited that Fluoride may lead to:
- Inhibit certain enzymes (e.g., enolase in glycolysis).
- Alter mitochondrial enzymes function at high concentrations.

These effects are typically seen at concentrations far exceeding typical dietary intake.

B. Oxidative Stress and Cellular Metabolism:

Fluoride exposure at high levels has been associated with:

- Lipid peroxidation.
- Increased reactive oxygen species (ROS).
- Altered antioxidant enzymes activity (e.g., catalase, superoxide dismutase).

This oxidative stress may underlie some endocrine and metabolic changes (Chlubek& Poland, 2003).

8. Dose, Duration, and Risk Assessment:

Biological effects of sodium fluoride depend strongly on dose (amount consumed), duration (in acute and chronic exposure), and individual susceptibility. risk assessment evaluates whether exposure levels pose a meaningful health concern (González-González *et al.*, 2025).

I. Dose:

Kabir *et al.* (2020) expressed that the magnitude of exposure is a critical determinant in toxicology, as reflected in the fundamental principle: *"The dose makes the poison."* In the case of NaF, exposure levels are typically quantified in milligrams per day (mg/day) or in milligrams per kilogram of body weight per day (mg/kg/day), allowing for accurate assessment of potential biological effects relative to individual body mass. Typical exposure levels, including the primary sources of fluoride and their estimated intake, are summarized in Table (2).

Table (2): Typical Exposure Levels:

Source	Approximate Fluoride Intake
Fluoridated water (0.7 mg/L)	1.5–3 mg/day (adults)
Toothpaste (incidental swallowing)	Small, variable
Naturally high-fluoride water (>3 mg/L)	Can exceed 6–10 mg/day

A. Regulatory Safety Thresholds:

Major health agencies have established intake guidelines:

- **Adequate Intake (AI):**
  - Adult men: ~4 mg/day.
  - Adult women: ~3 mg/day.
- **Upper Intake Level (UL):**
  - Adults: 10 mg/day.
  - Children: lower, based on age.
- **EPA Maximum Contaminant Level (MCL):**
  - 4.0 mg/L (to prevent skeletal fluorosis).
  - 2.0 mg/L (secondary standard to prevent dental fluorosis).

Margin of Safety: Public health water fluoridation guidelines are formulated with a considerable safety margin below established toxicity thresholds. This strategy provides a meaningful protective buffer between recommended exposure levels and those linked to potential adverse health outcomes. These reference limits are intended to safeguard individuals against harmful effects throughout a lifetime of exposure (Prystupa, 2011).

II. Duration: In Acute and Chronic Exposure:

A. Acute Exposure (Short-Term, High Dose):

Acute toxicity occurs at much higher doses.

- **Probable toxic dose:** ~5 mg/kg body weight (single ingestion)**.**
- **Symptoms:**
  - Nausea
  - Vomiting
  - Abdominal pain
  - Electrolyte imbalance (especially calcium)

- In severe cases: cardiac arrhythmia

Acute toxicity is rare and typically accidental (e.g., ingestion of large amounts of dental products or industrial exposure) (Whitford, 2011).

B. Chronic Exposure (Long Term and Lower Dose):

Chronic exposure effects depend on sustained intake above optimal levels.

- **Dental Fluorosis:**
  - Occurs during tooth development (children under 8).
  - Mild white streaking to brown discoloration.
  - Most common adverse effect at slightly elevated intake.
- **Skeletal Fluorosis:**
  - Occurs after years of high intake (>3–6 mg/L water).
  - Bone thickening and joint stiffness.
  - Advanced cases: pain and limited mobility.
- **Potential Endocrine and Metabolic Changes:**

  Seen mainly in high-exposure populations:
  - Altered thyroid hormone levels (especially in iodine deficiency).
  - Changes in bone metabolism (PTH activity).
  - Oxidative stress markers.

  At recommended fluoridation levels, these effects are not consistently observed (Sharma *et al.*, 2023).

III. Risk Assessment Framework:

EFSA Scientific Committee, *et al.* (2025) clarified that the risk assessment includes four main steps:

- **Step 1: Hazard Identification (Fluoride can affect):**
  - Teeth and bones.
  - Thyroid function.
  - Calcium metabolism.
  - Enzyme systems at high doses.
- **Step 2: Dose Response Assessment (Research shows):**
  - Low dose → beneficial for dental enamel.
  - Moderate excess → dental fluorosis.
  - High chronic dose → skeletal fluorosis.
  - Very high acute dose → systemic toxicity.

  The dose-response curve shows a **threshold effect** for most adverse outcomes.
- **Step 3: Exposure Assessment (Exposure depends on):**
  - Drinking water concentration.
  - Climate (higher intake in hot regions).
  - Diet (tea, seafood may contain fluoride).
  - Kidney function (fluoride excreted renally).
  - Age and body weight.
- **Step 4: Risk Characterization:**
  - **At 0.7 mg/L (standard fluoridation level):**
    - Dental benefit: High.
    - Risk of severe fluorosis: Low.
    - Risk of skeletal fluorosis: Extremely low.
    - Systemic endocrine risk: Not consistently demonstrated in healthy populations.

- **At > 3 – 4 mg/L over decades:**
  - Clear increased risk of skeletal fluorosis.
  - Possible thyroid alterations (context-dependent).
  - Higher total body burden.

9. Controversies and Debates in Fluoride Biology:

Fluoride's dual role as a preventive agent in dental health and a potential systemic toxin has fueled ongoing debate in fluoride biology. While its efficacy in reducing dental caries is well established, concerns persist about possible effects on bones, thyroid function, and metabolism at elevated exposures. This balance between benefit and risk remains central to the scientific discussion (Samaranayake *et al.*, 2025).

Individual susceptibility and environmental variability further complicate risk assessment. Age, nutritional status, kidney function, and naturally high fluoride levels in water can influence absorption, distribution, and biological effects. Reports from high-fluoride regions indicate increased incidences of skeletal and dental fluorosis and subtle endocrine disruptions, emphasizing the need for context-specific evaluation of safe exposure levels (Do *et al.*, 2025; Samaranayake *et al.*, 2025).

Public health policies reflect these tensions. Advocates highlight the protective dental benefits and established safety margins, while critics urge more research on long-term, low-dose exposure, particularly regarding endocrine and neurological effects. The debate highlights the necessity of balancing population-level benefits with individual health considerations, underscoring the importance of ongoing monitoring and research in fluoride biology (Do *et al.*, 2025; Samaranayake *et al.*, 2025; Wan, 2025).

10. Methodologies for Studying Fluoride Effects:

Research on fluoride's biological impact employs a combination of complementary approaches:

- **In Vitro Studies:** Utilize cultured cells (osteoblasts, odontoblasts, endocrine cell lines) to investigate molecular and cellular mechanisms, including enzyme activity, oxidative stress, and gene expression. Allow precise control of dose and exposure duration (Lavanya *et al.*, 2024).
- **Animal Models:** Rodents, canines, and primates are used to study systemic effects such as bone development, tooth mineralization, thyroid function, and metabolism. Chronic exposure studies provide insights into cumulative effects and tissue-specific toxicity (Ottappilakkil *et al.*, 2023).
- **Epidemiological and Human Studies:** Cross-sectional and longitudinal studies correlate environmental fluoride exposure with health outcomes (dental/skeletal fluorosis, thyroid function, metabolic markers). Biomonitoring of fluoride in blood, urine, hair, and bone quantifies internal dose (Taher *et al.*, 2024; Tiwari *et al.*, 2023).
- **Computational Modeling and Risk Assessment:** Integrates exposure data, toxicokinetics, and dose-response relationships to predict population-level risks and support public health guidelines (Soleimani *et al.*, 2026; Saxena *et al.*, 2025; Islam *et al.*, 2024; Sandoval-Pauker *et al.*, 2023).

Together, these methodologies form a robust framework for understanding fluoride's effects at molecular, organismal, and population levels (Martinez-Mier *et al.*, 2025; Sotili *et al.*, 2025).

11. Protective and Mitigating Strategies:

Sodium fluoride can exert adverse effects on the body at elevated exposures, necessitating strategies to minimize potential toxicity. The first line of protection is controlled exposure management, including adherence to recommended levels in drinking water (≈0.7 mg/L), careful monitoring of fluoride concentrations in food and beverages, and limiting accidental ingestion of high-fluoride dental products. Regulatory oversight and public health policies play a key role in maintaining safe exposure thresholds and preventing chronic overexposure (Lubojanski *et al.,* 2023). Nutritional interventions represent another effective mitigating strategy. Adequate intake of essential minerals, particularly calcium, magnesium, and iodine, can reduce fluoride absorption and counteract its interference with bone and thyroid metabolism. Sufficient dietary antioxidants such as vitamins C and E, selenium, and polyphenols may also mitigate oxidative stress induced by fluoride exposure, supporting overall cellular resilience (Atri *et al.,* 2025).

Maintaining hydration and promoting renal health are critical, as the kidneys are the primary route for fluoride excretion. Finally, screening, monitoring, and community level interventions enhance protective strategies. Bio-monitoring of fluoride levels in plasma, urine, and hair can identify populations at risk, especially in areas with naturally high fluoride in groundwater. Public awareness campaigns and educational programs on safe use of fluoride-containing dental products can prevent accidental overexposure in children. Collectively, these strategies encompassing exposure control, nutritional support, and proactive monitoring provide a comprehensive approach to safeguarding human health while preserving the established dental benefits of fluoride (Naiel *et al.,* 2026; Singh & Roychoudhury, 2025).

12. Implications for Public Health Policy:

Kumar *et al*. (2024) statement that NaF is widely used in public health interventions, particularly in water fluoridation programs and dental care products, due to its proven efficacy in reducing dental caries. While its benefits are well-documented, public health policy must carefully consider both its advantages and potential risks to optimize outcomes and minimize harm. The following implications are central to policy development:

I. Oral Health Promotion and Disease Prevention:

Yeh *et al.* (2025), Gao *et al.* (2021), Clarkson & McLoughlin (2000) and Whelton *et al.* (2019) collectively reported that sodium fluoride (NaF) remains a cornerstone of preventive dentistry. Systematic reviews consistently demonstrate that maintaining optimal fluoride concentrations in drinking water (approximately 0.7 mg/L) significantly reduces the prevalence of dental caries across all age groups. Public health policies incorporating fluoride-based interventions can:

- Lower the overall burden of dental diseases.
- Reduce healthcare costs associated with restorative dental treatments.
- Improve quality of life, particularly in underserved populations with limited access to dental care.

II. Risk of Fluorosis and Exposure Management:

Dumpala Gao *et al.* (2025), Noronha (2024), Veneri *et al.* (2024) and Toumba *et al.* (2019) collectively emphasized that excessive fluoride exposure particularly during critical periods of early childhood development, predisposes individuals to dental and skeletal fluorosis. These findings carry important public health and regulatory implications, including:

- Establishing regulatory limits on fluoride concentrations in drinking water and consumer products.
- Monitoring total fluoride exposure from multiple sources (water, food, dental products, and supplements).
- Implementing educational campaigns to guide safe use of fluoride toothpaste and supplements, especially among children.

III. Equity and Access Considerations:

Aoun *et al.* (2018) announcement that public health policies must balance the benefits of fluoridation with equitable access:

- Communities without fluoridated water may experience higher rates of dental caries, highlighting disparities in oral health outcomes.
- Policy frameworks should consider cost-effectiveness analyses to prioritize fluoridation initiatives in areas with limited dental care infrastructure.

IV. Environmental and Occupational Health Policies:

Usuda *et al.* (2009) publication that fluoride can accumulate in soil and water through industrial discharges. Public health policy must integrate environmental safety measures, such as:

- Monitoring and regulating industrial fluoride emissions.
- Assessing ecological impacts of long-term fluoride exposure on populations relying on local water sources.

V. Evidence-Based Policy and Public Trust:

American dental association council on scientific affairs (2006) reported that public acceptance of fluoride-based interventions is strongly influenced by transparency and the effective communication of scientific evidence. Accordingly, policy frameworks should:

- Rely on robust, peer-reviewed evidence regarding safe and effective fluoride concentrations.
- Engage communities in decision-making processes to build trust and improve compliance.
- Address misinformation and provide clear guidance on the health benefits versus potential risks.

VI. Integration with Broader Public Health Strategies:

Madad *et al.* (2025) interpreted that sodium fluoride–based interventions should be integrated within, and complement, comprehensive oral health policy frameworks:

- Inclusion of regular dental check-ups, nutrition education, and promotion of oral hygiene.
- Coordination with maternal and child health programs to optimize fluoride exposure during critical developmental periods.
- Continuous surveillance of population dental health outcomes to guide policy adjustments.

Overall, sodium fluoride remains a highly effective public health tool for the prevention of dental caries, but its use requires careful regulatory oversight and risk management. Public health policy must balance efficacy, safety, and equity, integrating scientific evidence, environmental considerations, and community engagement. By doing so, policymakers can maximize the benefits of fluoride interventions while minimizing adverse outcomes, thereby promoting sustainable oral health at the population level (Anyikwa & Ogwo, 2025; Duffin *et al.*, 2022; Frazão, 2022).

13. Ethical and Environmental Perspectives:

Both Chavarria (2025) and Samaranayake *et al.* (2025) emphasized that sodium fluoride is extensively employed in public health initiatives, particularly community water fluoridation, for the prevention of dental caries. While its efficacy is well established, ethical considerations and environmental implications are critical when evaluating its systemic effects on human health. Policymakers must address both dimensions to ensure that interventions are safe, equitable, and sustainable.

I. Ethical Perspectives: Ning *et al.* (2026) highlighted the following considerations:

a) **Autonomy and Informed Consent**:
- Water fluoridation introduces fluoride to entire communities, sometimes without explicit individual consent.
- Ethical policies should balance public health benefits with respect for individual autonomy, ensuring that populations are informed about potential systemic effects of fluoride exposure, including dental and skeletal fluorosis.

b) Equity and Social Justice:
- Fluoride exposure is not uniform; vulnerable populations, such as children, pregnant women, and individuals with renal impairments, are more susceptible to adverse effects.
- Ethical policy frameworks should ensure equitable protection by adjusting fluoride levels, monitoring exposure, and providing alternative preventive measures for high-risk groups.
- Resource allocation should prioritize communities with limited access to dental care, reducing disparities in oral health outcomes.

c) Risk-Benefit Transparency:
- Public health authorities have an ethical obligation to communicate both benefits (dental caries prevention) and risks (fluorosis, potential systemic effects) of sodium fluoride.
- Transparent risk communication fosters public trust and informed participation in health programs.

II. Environmental Perspectives: Unde *et al.* (2018) underscored key environmental concerns, particularly with respect to:

a) Ecological Accumulation:
- Excess sodium fluoride released into water bodies, soil, or through industrial processes can accumulate in ecosystems.
- Policy implications include monitoring environmental fluoride levels and implementing regulations to limit contamination, protecting both human and wildlife health.

b) Indirect Health Impacts via the Environment:
- Contaminated water or food sources may expose populations to higher than intended fluoride levels, increasing the risk of systemic effects on bones, teeth, and soft tissues.
- Environmental surveillance and water treatment standards are essential to prevent overexposure.

c) Sustainable Public Health Practices:
- Integrating environmental monitoring with public health policies ensures that fluoride interventions remain safe and sustainable.
- Policies should consider lifecycle impacts of fluoride, from production and industrial discharge to end-user consumption, minimizing ecological harm while achieving health benefits.

III. Policy Recommendations from Ethical and Environmental Perspectives: Zelko (2019) emphasized critical environmental considerations, particularly in relation to:

a) Establish Safe Exposure Guidelines: Set evidence-based limits that consider both systemic health risks and ecological impact.

b) Implement Transparent Communication Strategies: Educate communities about benefits, risks, and safe usage of fluoride.

c) Monitor Vulnerable Populations: Regularly assess fluoride exposure among children, pregnant women, and individuals with health vulnerabilities.

d) **Environmental Surveillance:** Regularly test water, soil, and ecosystems to prevent fluoride accumulation.
e) **Community Engagement in Decision-Making:** Include public consultation in decisions about water fluoridation and fluoride policies to respect autonomy and ethical accountability.

14. Future Directions and Research Priorities:

As highlighted by Sotili *et al.* (2025), Sodium fluoride (NaF) constitutes a cornerstone of preventive public health strategies, particularly in dental care, owing to its well-established efficacy in reducing dental caries. However, its systemic effects on the human body, ranging from dental and skeletal fluorosis to potential impacts on soft tissues and endocrine function, necessitate continued rigorous investigation. Advancing the scientific understanding of sodium fluoride's biological effects is essential for refining public health policies, optimizing risk, benefit assessments, and ensuring the implementation of safe, evidence-based interventions. Future directions and research priorities should encompass the following areas:

a) **Dose-Response Relationships and Safe Exposure (Levels) Thresholds:** Veneri *et al.* (2023) and Duffin *et al.* (2022) have suggested that:
   - Despite decades of research, precise dose-response relationships for systemic fluoride exposure, particularly in vulnerable populations, remain incompletely defined.
   - **Research Priority:** Conduct longitudinal, multi-center studies to determine safe exposure thresholds for children, pregnant women, and individuals with pre-existing renal or thyroid conditions.
   - Investigations should integrate cumulative fluoride exposure from water, food, dental products, and industrial sources.

b) **Systemic Health Effects Beyond Dental Outcomes:** Chavarria (2025), Dumpala *et al.* (2025), Samaranayake *et al.* (2025) and Yeh *et al.* (2025) have collectively proposed that:
   - While the benefits of fluoride in preventing caries are well-established, its broader systemic effects on bone density, endocrine function, neurodevelopment, and renal health require further elucidation.
   - Research Priority: Employ epidemiological, clinical, and mechanistic studies to assess chronic fluoride exposure at environmentally relevant levels.
   - Research should differentiate between optimal, subclinical, and toxic exposure ranges to inform regulatory limits.

c) **Vulnerable Populations and Individual Susceptibility:** Chavarria (2025), Taylor *et al.* (2025), Yeh *et al.* (2025), Lubojanski *et al.* (2023), Buzalaf (2018) and Twetman *et al.* (2004) have collectively advanced the proposition that:
   - Genetic, developmental, and health-related factors may influence individual susceptibility to fluoride toxicity.
   - Research Priority: Investigate the role of genetic polymorphisms, nutritional status, and comorbidities in mediating fluoride metabolism and toxicity.
   - Targeted studies on pediatric populations, pregnant women, and patients with renal impairment will improve risk stratification and guide personalized public health recommendations.

d) **Environmental Exposure and Indirect Health Impacts:** Pérez-Vega *et al.* (2026), Sotili *et al.* (2025), Maftouh *et al.* (2024), Lubojanski *et al.* (2023), Ahmad *et al.* (2022) and Harrison (2005) have convergently articulated the hypothesis that:
   - Environmental fluoride accumulation from industrial sources or natural contamination can contribute to unintended systemic exposure.

- Research Priority: Integrate environmental and epidemiological studies to quantify indirect exposure pathways and their health consequences.
- Developing predictive models of environmental fluoride transfer into food and water systems will inform both ecological and human health risk assessments.

e) **Innovative Monitoring and Biomarker Development**: González-González *et al.* (2025). Xiong Idowu *et al.* (2024), Idowu *et al.* (2021) and Lavalle-Carrasco *et al.* (2021) have collectively advanced a coherent line of evidence supporting the hypothesis that:

- Current approaches to measuring fluoride exposure are often limited to water levels or urinary fluoride, which may not fully reflect long-term systemic burden.
- Research Priority: Develop and validate reliable biomarkers for cumulative fluoride exposure and early detection of fluorosis or other systemic effects.
- Advances in non-invasive biomonitoring (e.g., hair, nails, saliva) could enable large-scale population surveillance and timely intervention.

f) **Evidence-Based Public Health Policy and Risk Communication:** Dumpala *et al.* (2025), Veneri *et al.* (2024), Dietrich-Leurer *et al.*(2023) and Gao *et al.* (2021) have jointly contributed to a growing and methodologically robust body of evidence substantiating the hypothesis that:

- Translating research findings into safe and effective public health interventions requires ongoing policy evaluation.
- Research Priority: Conduct policy-oriented research to assess the impact of different fluoride interventions, public perception, and compliance, with a focus on ethical and equitable implementation.
- Studies should explore strategies for balancing population-level benefits with the prevention of adverse systemic effects.

Briefly, future research on sodium fluoride must move beyond its established dental benefits to comprehensively address systemic effects, environmental pathways, and population heterogeneity. Priority areas include defining safe exposure limits, understanding individual susceptibility, developing robust biomarkers, and integrating environmental and epidemiological evidence. By targeting these research directions, policymakers and health professionals can optimize fluoride use, safeguard public health, and ensure interventions are both effective and ethically sound (Thompson, 2025; Mansur, 2023; Medjedovic *et al.*, 2015).

15. Conclusion:

This comprehensive scientific review has integrated current knowledge on the effects of sodium fluoride across multiple levels of biological organization, from molecular and subcellular components to cells, tissues, organs, and overall physiological systems. By analyzing its chemical properties and exposure pathways, the review underscores how environmental, dietary, occupational, and industrial sources collectively shape systemic fluoride levels and biological responses. Sodium fluoride exerts its effects through complex biochemical interactions, including modulation of enzyme activity, oxidative stress pathways, mitochondrial function, ion transport, and signaling cascades. At the cellular and subcellular levels, it impacts membrane integrity, protein structure, nucleic acid stability, and organelle function, with outcomes that depend on concentration, exposure duration, and biological context. At tissue and organ levels, systemic effects are observed in calcified tissues, endocrine organs, renal clearance systems, and neural structures, while developmental and neurobiological factors highlight the increased vulnerability of rapidly developing tissues during prenatal and early postnatal periods.

Dose response relationships, exposure duration, and population variability remain central to risk assessment, and distinguishing therapeutic benefits particularly for dental health from potential systemic toxicity requires careful interpretation of experimental, clinical, and epidemiological evidence. Methodological advances, such as molecular profiling, biomonitoring, mechanistic in vitro models, and longitudinal epidemiological studies, have strengthened understanding while revealing critical knowledge gaps. Protective and mitigating strategies including exposure monitoring, optimized fluoride concentrations, nutritional modulation, and public health surveillance are essential for balanced risk management. From a public health policy perspective, evidence-based regulation must consider toxicological thresholds, vulnerable populations, ethical responsibilities, and environmental sustainability, ensuring transparency, equitable access to safe water, and careful evaluation of ecological fluoride accumulation.

Looking forward, future research priorities should focus on refining low-dose and chronic exposure models, clarifying neuro-developmental outcomes, improving biomarker specificity, integrating systems biology approaches, and strengthening global exposure assessment frameworks. Interdisciplinary collaboration will be critical to resolving uncertainties and harmonizing international guidelines. In summary, sodium fluoride is a biologically active compound with context-dependent effects that can range from beneficial to potentially harmful. A nuanced, evidence-based, and ethically grounded approach is essential to ensure that its applications in public health maximize therapeutic benefits while minimizing biological and environmental risks.

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