January 2026
EPA-821-P-26-001

# Fluoride [CASRN 7782-41-4] Human Health Toxicity Assessment: Preliminary Assessment Plan and Literature Survey

January 2026

# Preliminary Assessment Plan and Literature Survey for the Fluoride Human Health Toxicity Assessment

Prepared by:

U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
Drinking Water Science and Engineering Division

Washington, DC 20460

EPA Document Number: EPA-821-P-26-001

# Disclaimer

This document is a public comment draft for review purposes only. This information is distributed solely for the purpose of public comment. It does not represent and should not be construed to represent any Agency determination or policy. References to entity names, commercial products, or trademarks are for factual purposes only and are not an endorsement by the United States Government or U.S. Environmental Protection Agency of these entities or their products, services, or enterprises.

# Acknowledgments

This document was prepared by the Drinking Water Science and Engineering Division (DWSED), Office of Ground Water and Drinking Water (OGWDW), Office of Water (OW) of the U.S. Environmental Protection Agency (EPA). The agency gratefully acknowledges the valuable contributions of EPA scientists from OW, including Elizabeth Radke (lead), Thomas Bateson (co-lead), Todd Zurlinden (co-lead), Krista Christensen, Paige Bommarito, Michael Dzierlenga, Carlye Austin, Bevin Blake, Czarina Cooper, Laura Dishaw, Lindsey Foote, Brittany Jacobs, Alexandra Lee, Casey Lindberg, Kelsey Miller, Hongyu Ru, Marie Russell, Rachel Shaffer, Avanti Shirke, Anthony Su, J. Michael Wright, and Erin Yost. The agency also gratefully acknowledges the valuable management oversight and review provided by Colleen Flaherty, Susan Euling, and Terra Haxton.

The systematic literature search and screening included in this document was prepared in collaboration with ICF under the U.S. EPA Contracts 68HERC23D0003. ICF contributors included Samantha Snow, Meredith Clemons, Sorina Eftim, Alexander Lindahl, Wren Tracy, Janielle Vidal, and Kate Weinberger.

# Contents

# Tables

# Figures

# Acronyms and Abbreviations

| | |
|---|---|
| ADA | American Dental Association |
| ADME | absorption, distribution, metabolism, and excretion |
| AI | artificial intelligence |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMDL | benchmark dose lower confidence limit |
| BMR | benchmark response |
| CalEPA | California Environmental Protection Agency |
| CASRN | Chemical Abstracts Service registry number |
| CDC | Centers for Disease Control and Prevention |
| EFSA | European Food Safety Agency |
| EPA | Environmental Protection Agency |
| F | fluorine |
| $F^-$ | fluoride ion |
| HA | Health Advisory |
| HC | Health Canada |
| HERO | Health and Environmental Research Online |
| HHRA | Human Health Risk Assessments |
| IQ | intelligence quotient |
| IARC | International Agency for Research on Cancer |
| IPCS | International Programme on Chemical Safety |
| IRIS | Integrated Risk Information System |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MeSH | medical subject headings |
| MRL | minimal risk level |
| NIEHS | National Institute of Environmental Health Sciences |
| NOAEL | no-observed-adverse-effect level |
| NPDWR | National Primary Drinking Water Regulation |
| NRC | National Research Council |
| NTP | National Toxicology Program |
| OEHHA | Office of Environmental Health Hazard Assessment |
| OPP | Office of Pesticide Programs |
| OW | Office of Water |
| PBPK | physiologically based pharmacokinetic |
| PECO | populations, exposures, comparators, and outcomes |
| PFAS | per- and polyfluoroalkyl substances |
| PK | pharmacokinetic |
| POD | point of departure |
| RED | Reregistration Eligibility Decisions |
| REL | reference exposure levels |
| RfD | reference dose |
| $r_p$ | Pearson correlation coefficient |

| | | | |
|---|---|---|---|
| SDWA | Safe Drinking Water Act | TSCA | Toxic Substances Control Act |
| SEM | systematic evidence map | $UF_D$ | database uncertainty factor |
| SWIFT | Sciome Workbench for Interactive computer-Facilitated Text-mining | WHO | World Health Organization |
| SYR | Six Year Review | | |
| TDI | tolerable daily intake | | |

# Executive Summary

The U.S. Environmental Protection Agency (EPA) is committed to ensuring clean and safe drinking water for all Americans with the goal of protecting human health, including children's health. In response to concerns about fluoride in drinking water, EPA is developing a new human health toxicity assessment that will review scientific information on the potential health risks of fluoride in drinking water. The Preliminary Assessment Plan and Literature Survey (Assessment Plan) is the first step in developing the toxicity assessment. The Assessment Plan outlines the scoping and problem formulation for the assessment. This Assessment Plan is not a toxicity assessment; it does not contain conclusions regarding harmful human health effects of fluoride or determine the levels of fluoride exposure associated with harmful health effects. Such conclusions about fluoride human health effects (e.g., toxicity values) will be released as part of the forthcoming draft human health toxicity assessment. The new EPA toxicity assessment will focus on the potential harmful health effects of fluoride exposure and will not consider beneficial effects such as dental caries prevention. When the toxicity assessment is final, EPA will have an updated scientific foundation that can inform future steps under the Safe Drinking Water Act (SDWA). By initiating the development of the new fluoride toxicity assessment, EPA is on track to finalize the assessment well before the next Six Year Review of the National Primary Drinking Water Regulations (NPDWR) under SDWA. The final toxicity assessment will also be used to inform Centers for Disease Control and Prevention (CDC) recommendations regarding fluoride in drinking water (Make America Healthy Again Commission, 2025). The decision whether or not to add fluoride to drinking water is made on a state or local basis; EPA does not make recommendations on adding fluoride to drinking water.

***Background.*** EPA Office of Water (OW) last published an evaluation of the potential harmful health effects associated with oral fluoride exposure in 2010 (U.S. EPA, 2010a). In that assessment, EPA determined that severe dental fluorosis, characterized by abnormal enamel development in children, was the most sensitive harmful human health effect (i.e., occurring at the lowest fluoride exposure levels) and therefore, was used to derive the toxicity value. In Six Year Review (SYR) 4 (U.S. EPA, 2024d), EPA concluded that the NPDWR for fluoride was not a candidate for revision due to the need to evaluate emerging research on neurodevelopment and cognition in children, which was under review by the National Toxicology Program (NTP) at that time. In the SYR4 report, EPA committed to considering the NTP (2024) report on neurodevelopment and cognition (when final) to inform the development of a new EPA fluoride toxicity assessment. To prepare for SYR5, EPA is developing a new fluoride toxicity assessment that considers all of the available peer-reviewed literature. The objective of the toxicity assessment is to determine the fluoride levels that a person can be exposed to and be unlikely to experience harmful health effects; these values are called toxicity values, specifically noncancer reference doses (RfDs).

***Gold Standard Science.*** EPA is systematically reviewing the literature on fluoride health effects, consistent with Gold Standard Science (Executive Order 14303) (United States Executive Office of the President Donald Trump, 2025) and the agency's peer-reviewed methods (U.S. EPA, 2022). EPA's systematic review process helps ensure that agency assessments are transparent,

reproducible, and uphold scientific integrity. It promotes incorporation of the best available, unbiased, peer-reviewed studies through broad literature searches in scientific databases. Additionally, EPA's systematic review process requires collaboration and contributions by many subject matter experts, which reduces potential for bias and error.

***Assessment Plan Objectives.*** As the first step in developing the toxicity assessment, OW is releasing the Assessment Plan for public comment to provide transparency and gather early feedback. The objectives of this document are to describe the approach EPA intends to follow to develop the human health toxicity assessment and present the results of the preliminary literature survey. As part of scoping and problem formulation, EPA also identified key science issues specific to fluoride exposure and health effects measurement that will be evaluated during toxicity assessment development.

***Preliminary Assessment Scope.*** The Assessment Plan outlines the scoping and problem formulation for the assessment, which was informed by scientific consensus to ensure a focused, fit-for-purpose toxicity assessment. EPA critically reviewed recent, peer-reviewed fluoride health effects reports published by multiple health agencies in order to determine scientific consensus about the types of harmful health effects associated with fluoride exposure. From reviewing these documents, EPA identified two well-established children's health effects (dental fluorosis and developmental neurotoxicity) as the most sensitive (i.e., occurring at the lowest exposure levels) harmful health effects associated with fluoride exposure (EFSA Scientific Committee, 2025; Health Canada, 2024; NTP, 2024). EPA's assessment will focus on identifying the most relevant studies of dental fluorosis and developmental neurotoxicity to derive an RfD. EPA's toxicity assessment will also use human data rather than animal (e.g., rat, mouse) toxicity data, which avoids the need to account for differences between animals and humans and reduces the overall uncertainty in the RfD. Additionally, EPA will identify and evaluate studies on how fluoride moves through the body (pharmacokinetic information or models) to help determine the RfD.

***Preliminary Literature Survey Results.*** The literature survey describes the results of conducting initial systematic review steps to identify relevant health effects studies, consistent with agency human health risk assessment guidance and Gold Standard Science (United States Executive Office of the President Donald Trump, 2025). EPA conducted a comprehensive, preliminary literature survey of the published, peer-reviewed data. Starting with literature search results of 268,967 unique references, artificial intelligence and other automated tools were used to efficiently prioritize the set of studies most likely to be relevant to the toxicity assessment. This was followed by traditional manual screening of the studies by health science experts. Through the systematic review steps performed to date, EPA has identified 562 human studies examining dental fluorosis (n = 489) and neurodevelopmental outcomes (e.g., cognition, behavior, and sensory/motor effects) (n = 98). The literature survey results can be transparently reviewed using a user-friendly application that allows the public to search, sort, and follow the studies throughout every step of the review.

***Next Steps.*** EPA is accepting public comments on this Assessment Plan for 30 days. EPA will consider all public comments during the next step in the toxicity assessment process, which is the development of the Systematic Review Protocol (Protocol). The Protocol will present detailed

methods for conducting the subsequent steps of the systematic review. EPA will then follow the Protocol to develop a draft Fluoride Human Health Toxicity Assessment (called the *toxicity assessment* herein). The draft toxicity assessment will follow EPA human health risk assessment methods and guidance, summarize the health effects associated with exposure to fluoride during childhood, and identify the fluoride level at or below which a person can be exposed to and be unlikely to experience harmful health effects. The draft toxicity assessment will be released for external peer review and public comment. EPA will consider the external peer review and public comments and revise the assessment as appropriate, prior to publishing a final Fluoride Human Health Toxicity Assessment.

# 1. Introduction

The U.S. Environmental Protection Agency (EPA) Office of Water (OW) is working expeditiously to develop a new, gold standard human health toxicity assessment (called the *toxicity assessment* herein) based on a systematic review of studies on harmful health effects associated with fluoride exposure (U.S. EPA, 2025a). The purpose of the toxicity assessment is to derive a final noncancer toxicity value for oral fluoride exposure, called the reference dose (RfD). The RfD is an estimate of the amount of a chemical below which a person can ingest daily over a lifetime that is unlikely to lead to harmful health effects.

As the first step in developing the toxicity assessment, OW is releasing this **Preliminary Assessment Plan and Literature Survey** for fluoride for public comment to provide transparency and gather early feedback (https://www.regulations.gov, Docket ID No. EPA-HQ-OW-2025-3823). This document outlines the approach EPA intends to follow to systematically review health effects studies for fluoride to develop the toxicity assessment.

EPA's fluoride toxicity assessment will evaluate human health hazards. It will not be a risk assessment, as it will not include an exposure assessment or an overall risk characterization nor will it address the legal, policy, social, economic, or technical considerations involved in risk management. The toxicity assessment, once final, can be used by EPA, states, Tribes, and local communities, along with specific exposure and other relevant information, to determine, under the appropriate regulations and statutes, the potential risk associated with human exposures to fluoride.

Specifically, EPA's toxicity assessment will be used to inform future decisions about potential revisions to the existing fluoride drinking water standard under the Safe Drinking Water Act (SDWA). The results of this toxicity assessment will also be used to inform Centers for Disease Control and Prevention (CDC) recommendations regarding fluoride in drinking water (Make America Healthy Again Commission, 2025).

EPA is using systematic review methods (U.S. EPA, 2022) to conduct a gold standard assessment of fluoride toxicity. Systematic review is a structured and documented process to identify, collect, and critically evaluate studies and data using explicit, pre-specified methods. It enhances consistency, transparency, and reproducibility; promotes use of the best available science and reduces bias; and upholds scientific integrity. Using systematic review methods ensures consistency with Executive Order 14303, Restoring Gold Standard Science and Gold Standard Science objectives (United States Executive Office of the President Donald Trump, 2025) and uses the "best available science" in accordance with sound and objective scientific practices (*see* SDWA 1412(b)(3)(A)(i) (U.S. EPA, 2020)). Through broad searches of the scientific literature databases, systematic review promotes identification of the best available, unbiased, peer-reviewed studies. Additionally, EPA's systematic review process requires collaboration and contributions by many subject matter experts, which reduces potential for bias and error.

To define the focus of the systematic review, EPA first performed a critical review of recent, peer-reviewed assessments of fluoride published by multiple health agencies including the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP) (NTP, 2024), the European Food Safety Authority (EFSA) (EFSA Scientific Committee, 2025),

Health Canada (Health Canada, 2024), and EPA OW (U.S. EPA, 2010a). EPA's review of these documents identified consensus findings about health hazards. Two children's health outcomes, tooth weakening (dental fluorosis) and developmental neurotoxicity (e.g., decreased intelligence quotient (IQ)), were identified as well-established and sensitive health effects associated with fluoride exposure. EPA then conducted a comprehensive, preliminary literature survey to identify peer-reviewed scientific studies on dental fluorosis and/or developmental neurotoxicity.

This **Preliminary Assessment Plan and Literature Survey** contains a summary of EPA's preliminary plan for developing the fluoride toxicity assessment. It includes a description of EPA's justification for conducting the toxicity assessment, including background information on fluoride uses and potential human exposure routes (Section 2.1); problem formulation conclusions that define the focus of the toxicity assessment (Section 2.2); key areas of scientific complexity (Section 2.3); specific aims of the assessment, which are the steps that will be taken to accomplish the assessment objectives (Section 3); the criteria that EPA used to identify relevant data for the preliminary literature survey (Section 4.1); results of the preliminary literature survey (Section 4.2); and the next steps that EPA will take to complete the toxicity assessment (Section 5).

# 2. Scoping and Initial Problem Formulation

## 2.1. Background

This section provides a summary of background information on fluoride to provide context for the toxicity assessment and is not intended to be comprehensive. A brief overview is provided on how humans are exposed to fluoride and the history of fluoride regulation under SDWA. This is followed by a summary of EPA's critical evaluation of recent, peer-reviewed fluoride health effects reports published by multiple agencies to identify consensus health hazard findings.

### 2.1.1. Human Exposure to Fluoride

Fluorides are chemical compounds that contain the element fluorine (F). Fluorine is a highly reactive gas that does not occur in its pure elemental state in nature; instead, it primarily exists in compounds or as an ion. Examples of fluoride compounds include calcium fluoride, potassium fluoride, and sodium fluoride. The term "fluoride" can also be used to refer specifically to the fluoride ion ($F^-$). Fluorine accounts for approximately 0.09% of the Earth's crust, making fluorine the 13$^{th}$ most common element within the crust. Weathering of and leaching from fluorine-containing rock can lead to fluoride in surface water, groundwater, and/or soil. The composition and mineral content of underlying rock formations determines the subsequent levels of naturally occurring fluoride in surface water and/or groundwater (WHO, 2004; ATSDR, 2003). Industrial chemicals (that dissociate to $F^-$ in water) and fluoride supplementation of drinking water are two sources of fluoride in surface water and/or groundwater that originate from human activities.

Fluoride exposure to humans can occur through several pathways, including drinking water, food, consumer products, and air. It has been estimated that 40 to 70 percent of cumulative fluoride exposure in the United States is due to drinking water intake (U.S. EPA, 2010b). Many communities add fluoride (as fluorosilicic acid and sodium hexafluorosilicate (ATSDR, 2003)) to the public drinking water supply as a measure to prevent dental caries (i.e., cavities). Fluoride levels in groundwater and well water can be higher in geographic areas rich in naturally occurring fluoride-containing minerals, compared to municipal water supplies that rely on surface water as their primary source of drinking water. Trace amounts of fluoride have been found in vegetation (e.g., dark, leafy greens and tea leaves), as fluoride can be absorbed from soil and fertilizers (Huang et al., 2025). Exposure of the general population to airborne fluoride is expected to be low relative to ingested fluoride, although exceptions could include populations living near industrial sites (U.S. EPA, 2010b; NRC, 2006). Exposure to fluoride can also occur through the use of dental care products (e.g., toothpaste and mouthwash), or fluoride-containing dietary supplements or medications (NIH, 2025; ATSDR, 2003).

### 2.1.2. Safe Drinking Water Act National Primary Drinking Water Regulation

Fluoride exposure has been associated with both beneficial and harmful effects on human health, depending on the amount of exposure. At lower levels, fluoride has been shown to decrease the prevalence of tooth decay (dental caries/cavities), one of the most common chronic diseases among American children (CDC, 2024). Higher levels of fluoride exposure can result in harmful

effects on permanent (adult) teeth called dental fluorosis in children, which can range from mild (small white striations or opaque areas) to severe (pitting) (U.S. EPA, 2010a). Additionally, a recent systematic review by NTP (2024) concluded that there is moderate confidence that exposure to fluoride at levels greater than 1.5 mg/L in drinking water is associated with lower IQ in children, with a similar finding based on fewer data and with greater uncertainty at lower levels of exposure (e.g., less than 1.5 mg/L in drinking water). Prolonged higher levels of fluoride intake are associated with an increased prevalence of bone weakening, called skeletal fluorosis, across all lifestages which can include brittle bones, increased risk of fractures, and crippling (severe bone abnormalities) (U.S. EPA, 2010a; Dean, 1942).

In the United States, fluoride in public water systems is regulated as a drinking water contaminant under SDWA. EPA's current fluoride National Primary Drinking Water Regulation (NPDWR) was established in 1986 (U.S. EPA, 1986b) with a maximum contaminant level (MCL) and maximum contaminant level goal (MCLG) of 4 mg/L to protect against crippling (stage III)[1] skeletal fluorosis. EPA also established a secondary MCL of 2 mg/L to protect against cosmetically objectionable dental fluorosis in children. Secondary MCLs are non-enforceable levels which are set at a level that does not present a risk to human health but may address aesthetic, technical, and/or cosmetic considerations.

EPA does not make recommendations on adding fluoride to drinking water, since SDWA prohibits EPA from requiring the addition of any substance to drinking water for preventive health care purposes (Section 1412(b)(11)) (U.S. EPA, 2020). For communities that add fluoride to their water systems, the U.S. Public Health Service recommends an optimal fluoride concentration of 0.7 mg/L to provide protection against dental caries while limiting the risk of adverse effects such as dental fluorosis (U.S. Department of Health and Human Services, 2015). The decision whether or not to add fluoride to drinking water is made on a state or local basis.

As part of the Six Year Review (SYR) of NPDWRs required under SDWA, EPA has reviewed the fluoride drinking water standard several times. Following SYR1 in 2003 (U.S. EPA, 2003), EPA requested a review of fluoride health effects data by the National Research Council (NRC) of the National Academies of Science (NRC, 2006). The NRC recommended that EPA lower its MCLG, concluding that it was not protective against severe dental fluorosis and may not be protective against increased bone fractures. In response, in 2010, EPA released its updated fluoride dose-response analysis for noncancer effects (scoped to dental fluorosis, skeletal fluorosis, including skeletal fractures) and derived an RfD of 0.08 mg/kg/day (U.S. EPA, 2010b) based on the critical effect of severe dental fluorosis in a human epidemiological study Dean (1942). This RfD is protective against skeletal fluorosis, specifically clinical stage II[1] and skeletal fractures. In SYR3 (U.S. EPA, 2016), published in 2017, EPA identified a potential MCLG range of 0.9–1.2 mg/L based on the agency's 2010 assessment conclusions U.S. EPA (2010a). In SYR3, the NPDWR for fluoride was not deemed a candidate for revision due to identification of other

[1] From NRC (NRC, 2006), Stage III skeletal fluorosis is the most severe stage (often referred to as the "crippling" stage) and represents alterations in bone architecture and calcification of tissues that progress to the degree that they limit an individual's range of motion. Stage II skeletal fluorosis is the stage before mobility is significantly affected, but is characterized by chronic joint pain, arthritic symptoms, slight calcification of ligaments, and osteosclerosis of the cancellous bones.

significant NPDWRs of higher agency priority (U.S. EPA, 2017). In SYR4, published in 2024, EPA identified a potential MCLG of 0.9 mg/L (U.S. EPA, 2024d). In SYR4, EPA concluded that the NPDWR for fluoride was not a candidate for revision due to ongoing high priority actions and emerging research on developmental neurotoxicity (U.S. EPA, 2024d). Specifically, EPA noted that future regulatory decision-making may be informed by NTP's *Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition* (NTP, 2024), which had not been finalized at the time of SYR4 publication (U.S. EPA, 2024c).

### 2.1.3. Critical Review of Recent Authoritative Reports on Toxicity

EPA conducted a critical review of recently published reports on fluoride toxicity from authoritative sources, including the NTP (2024) report. Critically reviewing these authoritative scientific reports allowed EPA to identify consensus findings about the types of harmful health effects that are affected by fluoride exposure.

NTP (2024) evaluated the evidence of an association between exposures to fluoride and human neurodevelopment and cognition, including human, animal, and mechanistic studies published through May 1, 2020, and included an addendum describing findings from papers on children's IQ published through October 2023. Based on its systematic review, which was limited to neurodevelopmental and cognitive effects, NTP concluded that there is moderate confidence that higher levels (e.g., greater than 1.5 mg/L in drinking water) of fluoride exposure are associated with lower IQ in children, with a similar finding based on fewer data and with greater uncertainty at lower levels of exposure (e.g., less than 1.5 mg/L in drinking water). The NTP Monograph did not develop a toxicity value (e.g., RfD) for fluoride, but a subsequent meta-analysis of epidemiological data by NTP authors (Taylor et al., 2025) provided a quantitative estimate of the decrease in children's IQ score per unit of fluoride exposure. The inverse association between fluoride exposure and decreased IQ remained consistent when data were stratified by study quality (high or low risk of bias), sex, country, exposure matrix (drinking water or urine), outcome assessment type, and prenatal or postnatal exposure.

The most recent and comprehensive final assessment of fluoride health effects was conducted by EFSA (EFSA Scientific Committee, 2025), which aimed to determine whether there are health effects that are more sensitive than dental outcomes that would necessitate revisions to the European Union health-based guidance values (HGBV) for fluoride. EFSA conducted a broad literature survey on the hazards of fluoride in humans and animals. From the large volume of literature that was identified, EFSA selected the following health outcome categories for full systematic review and hazard identification: neurotoxicity, due to concerns raised in recent years regarding the inverse association between fluoride exposure and neurodevelopmental toxicity (e.g., NTP (2024)); bone health (including bone cancer), which may be affected at lower exposure levels compared to skeletal fluorosis; and thyroid effects, which are of concern due to the similarity between fluoride and iodide (needed for the body to make thyroid hormones). EFSA did not perform hazard identification for dental or skeletal fluorosis since the association of these effects with fluoride exposure has already been extensively characterized. Consistent with NTP's findings (NTP, 2024), EFSA found that total fluoride intake was associated with adverse effects on the developing brain at drinking water concentrations greater than 1.5 mg/L but determined that the evidence at lower exposure levels was inconclusive (EFSA Scientific Committee, 2025).

EFSA concluded that dental fluorosis remained the most sensitive outcome in children up to 8 years old and derived a tolerable upper intake level in drinking water of 1.4 mg/L based on the data of Dean (1942), which EFSA anticipates being protective of all adverse effects including neurodevelopmental toxicity. Early childhood is considered the relevant exposure window for developing dental fluorosis as it corresponds with enamel development of the adult teeth. For age groups over 8 years old and adults including pregnant women, a reference point of 1.5 mg/L based on neurodevelopmental toxicity was used to derive a safe intake level of fluoride, which is also considered to be protective of bone and thyroid toxicity (EFSA Scientific Committee, 2025).

Health Canada also recently conducted a systematic review on the health hazards of fluoride drinking water exposure (Taher et al., 2024), which was presented to an expert panel for recommendations about dental fluorosis and neurocognitive development in children as sensitive endpoints of concern (Health Canada, 2024). The panel agreed with the use of the Dean (1942) study for derivation of a point of departure for dental fluorosis, specifically a 1% lower limit benchmark dose of 1.56 mg/L in drinking water. Additionally, a provisional point of departure for neurocognitive effects was proposed as 1.5 mg/L (Taher et al., 2024), but the panel concluded that there was insufficient information to recommend a specific point of departure for neurocognitive effects in children given the greater uncertainty regarding effects in the low dose range (Health Canada, 2024).

A summary of noncancer health effect reference values for chronic oral exposure to fluoride from EPA and other federal or international health agencies is presented in Table 2-1. In addition, EPA reviewed published reports from authoritative sources that evaluated the potential carcinogenicity of fluoride (Table 2-2). These published reports on cancer were identified by searching the recent authoritative reports on fluoride toxicity (Appendix A, Table A-1). These reports identified data gaps in the evaluation of carcinogenicity for fluoride that precluded a carcinogenicity determination.

**Table 2-1. Details on Derivation of the Available Noncancer Health Effect Reference Values for Chronic Oral Exposure to Fluoride by EPA and Other Agencies**

| Reference Value Source | Health Effect(s) | Reference Value(s) | Point of Departure (POD) | POD Type and Qualifier | Data Source | Total Uncertainty Factors |
|---|---|---|---|---|---|---|
| EPA Office of Water (OW) (U.S. EPA, 2010b) | Severe dental fluorosis | RfD = 0.08 mg/kg/day[a] | 1.87 mg/L | BMDL (based on BMR = 0.5%) | Dean (1942) | 1 |
| EPA Integrated Risk Information System (IRIS) (U.S. EPA, 1987) | Moderate and severe dental fluorosis | RfD = 0.06 mg/kg/day[b] | 1 mg/L | NOAEL | Hodge (1950) cited in Underwood (1977) | 1 |
| European Food Safety Agency (EFSA) (EFSA Scientific Committee, 2025) | Mild to severe dental fluorosis | Infants (< 1 year): UL = 1 mg/day (0.14 mg/kg/day)<br><br>Toddlers (1–3 years): UL = 1.6 mg/day (0.13 mg/kg/day)<br><br>Children (4–8 years): UL = 2 mg/day (0.1 mg/kg/day)[c] | 1.4 mg/L | BMDL (based on BMR = 5%) | Dean (1942) | 1 |
| | Central nervous system effects | "Safe intake level" for age groups > 8 years old and adults, including pregnant women = 3.3 mg/day[d] | 1.5 mg/L | Reference point above which adverse effects are consistently observed | Based on weight of evidence analysis | N/A |
| Health Canada (Health Canada, 2010) | Moderate to severe dental fluorosis | TDI = 0.105 mg/kg/day[e] | 1.56 mg/L | BMDL (based on BMR = 1%) | Dean (1942) | 1 |
| Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2003) | Skeletal effects (increased risk of bone fractures) | MRL = 0.05 mg/kg/day[f] | 0.15 mg/kg/day | NOAEL | Li et al. (2001a) | 3 (to account for human variability) |

| Reference Value Source | Health Effect(s) | Reference Value(s) | Point of Departure (POD) | POD Type and Qualifier | Data Source | Total Uncertainty Factors |
|---|---|---|---|---|---|---|
| California Office of Environmental Health Hazard Assessment (OEHHA) (OEHHA, 2008) | Moderate to severe dental fluorosis | REL = 0.04 mg/kg/day[g] | 1 mg/L | NOAEL | Dean (1942) | 1 |

EPA = Environmental Protection Agency; POD = point of departure; OW = Office of Water; RfD = reference dose; BMDL = benchmark dose lower confidence limit; BMR = benchmark response; IRIS = Integrated Risk Information System; NOAEL = no-observed-adverse-effect level; EFSA = European Food Safety Agency; UL = tolerable upper intake level; N/A = not applicable; TDI = tolerable daily intake; ATSDR = Agency for Toxic Substances and Disease Registry; MRL = minimal risk level; OEHHA = Office of Environmental Health Hazard Assessment; REL = reference exposure level.

[a] The EPA OW RfD was calculated by summing the estimated fluoride intake by children from drinking water at the BMDL (0.07 mg/kg/day, based on drinking water intake rates and body weights from the United States Department of Agriculture 1977/1978 Nationwide Food Consumption Survey (Ershow and Cantor, 1989)) and estimated dietary fluoride intake of 0.01 mg/kg/day (from McClure (1943)).

[b] The EPA IRIS RfD was calculated by summing the estimated fluoride intake by children from drinking water at the NOAEL (0.05 mg/kg/day, based on drinking water intake of 1 L/day for a 20 kg child) and an estimated dietary fluoride intake of 0.01 mg/kg/day.

[c] The EFSA ULs were calculated by summing the estimated fluoride intake by children from drinking water at the BMDL (1.12, 1.46, and 1.79 mg/day for children ages 6–12 months, 1–3 years, and 4–8 years; based on drinking water intakes of 0.8–1, 1.3, and 1.6 L/day for the three age groups and assuming that 20% of fluids will contain negligible fluoride levels) and 1940's era estimates of dietary fluoride intake (0.09, 0.12, and 0.20 mg/day for children ages 6–12 months, 1–3 years, and 4–8 years), with default body weights of 8.8, 12, and 20 kg for age groups 6–12 months, 1–3 years and 4–8 years, respectively. This is documented in Table 27 of EFSA Scientific Committee (2025).

[d] The EFSA "safe intake level" uses 1.5 mg/L in drinking water as the reference point above which there is consistent evidence of adverse neurodevelopmental effects in children. The safe intake level was calculated by summing the estimated fluoride intake from drinking water at 1.5 mg/L (2.4 mg/day, based on drinking water intake rate of 2 L/day for adult women and assuming that 20% of fluids contain negligible fluoride levels) with estimated fluoride intake from food (0.64 mg/day) and dental products (0.3 mg/day).

[e] The Health Canada TDI was calculated by summing the estimated fluoride intake by children from drinking water at the BMDL (98.5 µg/kg/day, based on 0.8 L/day for an 13 kg child) with estimated fluoride intake from food (5.4 µg/kg/day assuming a 1940s diet for a 1-to-4-year-old child), soil (1.19 µg/kg/day), and air (0.01 µg/kg/day).

[f] The ATSDR MRL was calculated based on the total daily fluoride intake reported by Li et al. (2001a) (3 mg/day at the NOAEL) and a reference body weight of 55 kg. An uncertainty factor of 3 was applied to account for variability in the human population (decreased from 10 because the NOAEL was derived from a sensitive subpopulation, i.e., elderly men and women).

[g] The California OEHHA REL was calculated from estimated fluoride intake by children from drinking water at the NOAEL, based on the assumption that an 18 kg child drinks 720 mL of water per day.

**Table 2-2. Cancer Conclusions from Exposure to Fluoride by EPA and Other Agencies**

| Source | Overview/Scope | Basis for Cancer Conclusion | Cancer Conclusions |
|---|---|---|---|
| European Food Safety Agency (EFSA) (EFSA Scientific Committee, 2025) | Toxicity assessment of fluoride in drinking water and food, mandated by the European Commission to update the previous EFSA fluoride assessment from 2005. Systematic review performed for bone cancer but not other types of cancer. | Descriptive conclusion based on the weight of evidence. No specific approach for deriving a cancer descriptor was followed. | Lack of association between fluoride exposure and bone cancer. Conclusions on other types of cancer not addressed. |
| California Office of Environmental Health Hazard Assessment (OEHHA) (OEHHA, 2011b) | Assessment of the evidence of carcinogenicity to inform deliberations on whether fluoride and its salts should be listed under California Proposition 65. Conclusions based on studies included in previous reviews of fluoride carcinogenicity by NRC (1993), NRC (2006), and ATSDR (2003) and supplemented by a relevant human epidemiological study published after NRC 2006 (Bassin et al., 2006). | Descriptive conclusion based on the weight of evidence. No specific approach for deriving a cancer descriptor was followed. | The California Proposition 65 Carcinogen Identification Committee concluded "fluoride and its salts has not been clearly shown to cause cancer" (OEHHA, 2011a). |
| Health Canada[a] (Health Canada, 2010) | Technical guidance document for fluoride used to develop Guidelines for Canadian Drinking Water Quality. | Health Canada criteria for classification of carcinogenicity.[b] Group VI corresponds with IARC Group 3, which corresponds to evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. | *Group VI: Unclassifiable with respect to carcinogenicity in humans*. |
| EPA Office of Pesticide Programs (OPP) (U.S. EPA, 2007), (U.S. EPA, 1996) | Reregistration Eligibility Decisions (RED) for the manufacture and use of sodium fluoride as a fungicide (used as a wood preservative in lumber and other wood products), and for the manufacture and use of cryolite (sodium aluminoflouride) as an insecticide on food crops. | Classification system described in EPA's 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a).[c] Group D is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available. | Sodium fluoride and sodium aluminoflouride are described as *Group D (not classifiable as to carcinogenicity).* |
| National Research Council (NRC) (NRC, 2006) | Review of fluoride data by the NRC of the National Academies of Science based on the request from EPA OW to assess the adequacy of the current drinking water standards under SDWA to protect human health. | Descriptive conclusion based on the weight of evidence. No specific approach for deriving a cancer descriptor was followed. | Based on "consideration of data from humans, genotoxicity assays, and studies of mechanisms of action in cell systems (e.g., bone cells *in vitro*), the evidence on the potential of fluoride to initiate or promote |

| Source | Overview/Scope | Basis for Cancer Conclusion | Cancer Conclusions |
|---|---|---|---|
| | | | cancers, particularly of the bone, is tentative and mixed." |
| World Health Organization (WHO) (WHO, 2004) | Background document for the development of guidelines for drinking water quality for fluoride by the WHO. | The document does not provide an independent conclusion but instead only notes agreement with IARC and IPCS. | The document notes agreement with the IARC conclusion of inadequate evidence of carcinogenicity in humans IARC (1987b) and the IPCS conclusion "that the evidence of carcinogenicity in laboratory animals is inconclusive and that the weight of evidence does not support the hypothesis that fluoride causes cancer in humans; however, the data on bone cancer are relatively limited." (IARC, 1987a) |
| Agency for Toxic Substances and Disease (ATSDR) (ATSDR, 2003) | Toxicological profile assessment for fluorides, hydrogen fluoride, and fluorine, including an assessment of cancer. | Neither a descriptive conclusion nor a formal cancer descriptor was provided. | Did not provide a conclusion but noted data gaps. "Additional studies are needed to further evaluate the potential of fluoride to induce bone cancers following chronic oral exposure." |
| International Agency for Research on Cancer (IARC) (IARC, 1987b) | Determination of cancer hazard for fluorides (inorganic, used in drinking water). | IARC Monograph hazard classifications.[d] Group 3 is used for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. | Fluorides (inorganic, used in drinking water) are described as *Group 3: Not classifiable as to its carcinogenicity to humans*. |

EPA = Environmental Protection Agency; EFSA = European Food Safety Agency; OEHHA = Office of Environmental Health Hazard Assessment; NRC = National Research Council; ATSDR = Agency for Toxic Substances and Disease Registry; IARC = International Agency for Research on Cancer; OPP = Office of Pesticide Programs; RED = Reregistration Eligibility Decisions; OW = Office of Water; SDWA = Safe Drinking Water Act; WHO = World Health Organization; IPCS = International Programme on Chemical Safety.

[a] Health Canada recently conducted a systematic review (Taher et al., 2024); they did not find additional evidence of an association between fluoride exposure and cancer, based on studies published between 2016 and 2021.

[b] Health Canada categories for classification of carcinogenicity are as follows: Group I (carcinogenic to humans), Group II (probably carcinogenic to humans), Group III (possibly carcinogenic to humans), Group IV (unlikely to be carcinogenic to humans), Group V (probably not carcinogenic to humans), and Group VI (unclassifiable with respect to carcinogenicity in humans).

[c] EPA 1986 categories for classification of carcinogenicity are as follows: Group A (carcinogenic to humans), Group B (probably carcinogenic to humans), Group C (possibly carcinogenic to humans), Group D (not classifiable as to human carcinogenicity), and Group E (evidence of noncarcinogenicity for humans).

[d] IARC Monographs hazard classifications for carcinogenicity are as follows: Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans), Group 3 (not classifiable as to its carcinogenicity to humans), and Group 4 (probably not carcinogenic).

## 2.2. Problem Formulation and Defining the Assessment Scope

Problem formulation is the step that reviews the available toxicity information in order to define the scope of a toxicity assessment and key science issues to address. This section describes how EPA used its critical review of recent, peer-reviewed reports on fluoride toxicity from multiple health agencies (see Section 2.1.3) and results from EPA's systematic review of the peer-reviewed scientific literature to narrow the scope of the toxicity assessment to human epidemiology studies of dental fluorosis and developmental neurotoxicity. EPA's review of these documents identified consensus findings about these two well-established noncancer children's health hazards. EPA's toxicity assessment will not include evaluation of cancer because there are data gaps that preclude a new carcinogenicity determination for fluoride (see Section 2.1.3). The potential health benefits of oral fluoride exposure (e.g., decreased dental caries) are not within the scope of this toxicity assessment because SDWA prohibits EPA from requiring the addition of any substance to drinking water for preventive health care purposes (Section 1412(b)(11)) (U.S. EPA, 2020).

The objective of the new toxicity assessment of fluoride is to derive an RfD (see Section 1) to protect human health. The agency implemented a robust systematic review process, based on EPA's externally peer-reviewed human health risk assessment methodology (U.S. EPA, 2022). The published literature on fluoride is vast, encompassing nearly a century of data on both adverse and beneficial health outcomes in humans, animal, and in vitro models, as well as pharmacokinetic data to inform the transport and elimination of fluoride within the body.

To develop a new human health toxicity assessment for fluoride, the agency deployed a multidisciplinary team of scientists, including epidemiologists, biologists, toxicologists, pharmacokinetic modelers, and statisticians, with expertise in systematic review and risk assessment to perform this first step of scoping and problem formulation. In this step, the team critically reviewed existing fluoride health effects published assessments and reports, performed a literature search of the available peer-reviewed databases and other resources, and conducted screening, prioritization, and sorting of 268,967 unique studies for fluoride. The team of scientists considered and then applied a variety of prioritization approaches and manually screened tens of thousands of references to identify those considered most likely to be informative to the toxicity assessment and subsequent toxicity value derivation (see Appendix B). The results of the literature search, prioritization, and screening were used to define the literature survey results, described below.

EPA refined the scope of the systematic review by critically evaluating recent fluoride health hazard documents by other authoritative bodies, including EFSA (EFSA Scientific Committee, 2025), Health Canada (Health Canada, 2024; Taher et al., 2024), and NTP (NTP, 2024) (see Section 2.1.3). The EFSA Scientific Committee (2025) conducted a broad literature survey of potential health outcomes and concluded that dental fluorosis and developmental neurotoxicity are the most sensitive outcomes in children based on the available data. The systematic review commissioned by Health Canada (Taher et al., 2024) similarly concluded that dental fluorosis and reduced IQ scores in children are the most relevant endpoints for dose-response analysis. The association between fluoride exposure and dental fluorosis has already been well-established and is supported by previous reports (Table 2-1). In its systematic review, NTP (2024) stated with

moderate confidence that fluoride exposure is inversely associated with children's IQ based on consistent results across different populations, study designs, geographic areas, and exposure sources and metrics.

To expedite the toxicity assessment development, EPA leveraged consensus hazard conclusions based on its critical review of the latest fluoride health science from EFSA (EFSA Scientific Committee, 2025), Health Canada (Health Canada, 2024; Taher et al., 2024), and NTP (NTP, 2024) rather than re-review the full set of literature to establish hazards for fluoride. Specifically, EPA is adopting well-established consensus hazard conclusions related to dental fluorosis and developmental neurotoxicity (as described below and in Section 2.1.3). Thus, the systematic review steps of evidence synthesis and integration are not necessary. Instead, EPA is focusing its resources and expertise on conducting a comprehensive literature search (Appendix B) with a focus on identifying the studies most suitable for dose-response analysis for these two key children's health outcomes. The study identification process has been made more efficient through the use of artificial intelligence (AI) and other automated tools in the prioritization of literature combined with traditional manual screening as described in Appendix B.2. The automated tools used for the literature survey are well-established for the systematic review of health effects literature and have been used to develop previous EPA toxicity assessments. For example, EPA used an AI tool called SWIFT-Active Screener (Howard et al., 2020) trained by subject matter experts to predict relevant references and expedite the screening of fluoride health effect studies. See Figure 2-1 for a visual of the fluoride assessment process and Figure 2-2 for a summary of how published authoritative reports inform the current assessment.

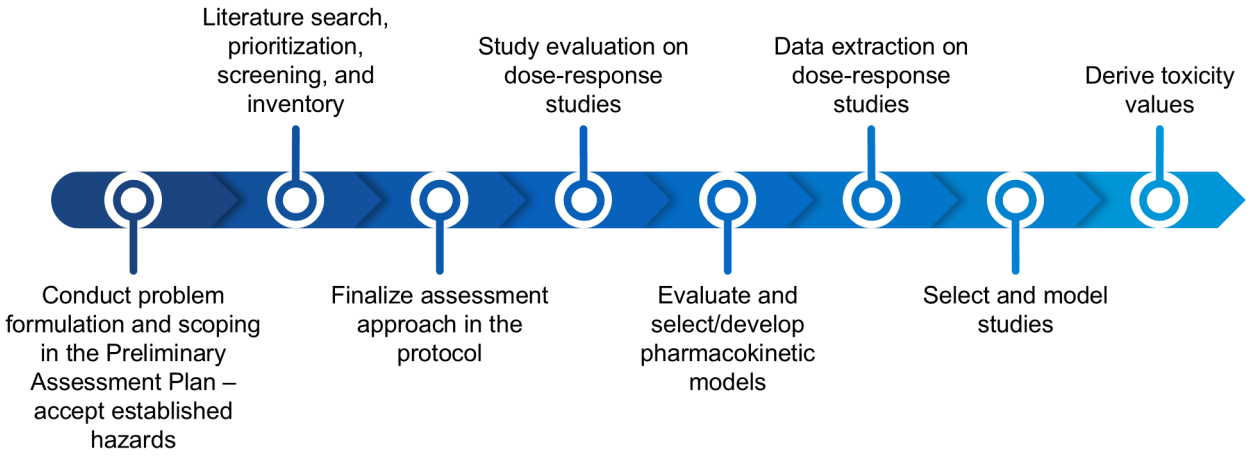


**Figure 2-1. Stages of EPA's Fluoride Assessment Development Process**

The scope of the dose-response analysis will be on two key children's health outcomes: dental fluorosis and developmental neurotoxicity. These two critical, sensitive health outcomes were identified by the EFSA Scientific Committee (2025) and Health Canada (Health Canada, 2024; Taher et al., 2024), and informed by NTP (2024). Additionally, EPA's updated assessment will focus on human studies only because of fluoride's large epidemiological health effects database. The use of epidemiological studies for deriving toxicity values eliminates uncertainties associated with interspecies extrapolation and for this reason, are preferred over animal data when robust studies are available (U.S. EPA, 2022). Furthermore, all previous final reports deriving

toxicity values for fluoride have been based on epidemiological data (Table 2-1), which provides additional support for scoping to human studies. For dose-response analysis of developmental neurotoxicity, EPA will critically evaluate the NTP meta-analysis of cognitive effects in children (Taylor et al., 2025) for possible use or adaptation in toxicity value derivation. The potential health benefits of oral fluoride exposure (e.g., decreased dental caries) are not part of conducting a human health toxicity assessment and will not be considered as part of EPA's dose-response analysis.

EPA generally sets the MCLGs at zero for contaminants that are known or likely carcinogens, unless the best available data show that there is a concentration below which cancer does not occur. In these cases, the MCLG is set at that lower level. Published assessments (Table 2-2) from health agencies have concluded that the data available from epidemiology and animal studies are insufficient to support a carcinogenicity determination for fluoride. NRC (2006) reviewed the available information on carcinogenicity after fluoride exposure at the request of EPA and determined that the evidence was tentative and mixed, and recommended that additional highly focused epidemiologic studies be conducted to assess specific tissues that have suggestions of carcinogenic activity based on the human and animal literature (i.e., osteosarcomas and cancers of the buccal cavity, kidney, bones, and joints). More recently, EFSA (EFSA Scientific Committee, 2025) concluded that the available evidence does not support an association between fluoride exposure and bone cancer, and the systematic review conducted on the behalf of Health Canada did not identify an association between fluoride exposure and cancer (Taher et al., 2024) (Table 2-2). As part of EPA's preliminary literature survey for fluoride, described here, an inventory of human and animal studies reporting on the development of cancer in any tissues following fluoride exposure was developed (Appendix C). EPA's literature survey identified a total of four animal toxicology studies and 23 epidemiology studies that reported on the association between fluoride exposure and cancer. All four animal cancer bioassays have been previously evaluated by the published reports. Of the 23 cancer epidemiology studies, four studies had not been previously evaluated by the published reports. The four newly identified human epidemiology studies (Table C-1) do not provide evidence of a positive association between fluoride exposure and carcinogenicity that would warrant further evaluation. Therefore, EPA's new toxicity assessment of fluoride will not include an evaluation of cancer.

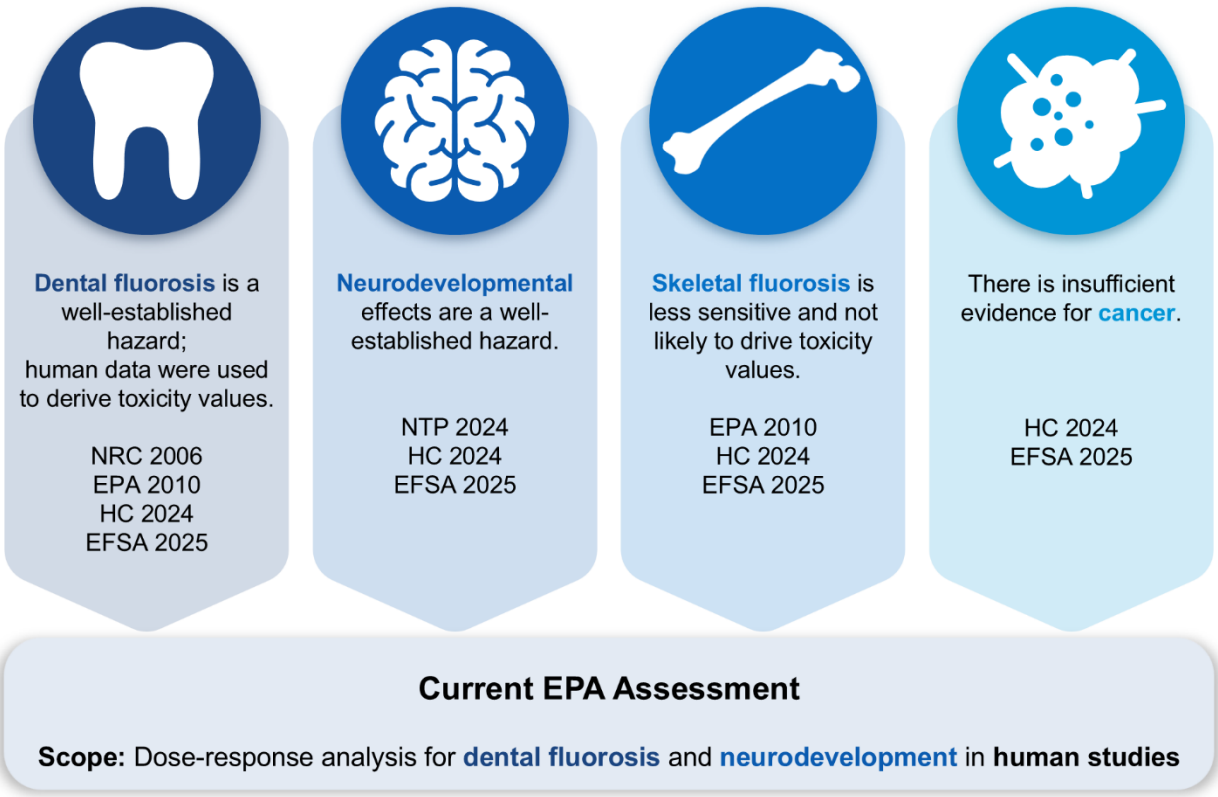


**Figure 2-2. Summary of Use of Previously Published Authoritative Reports to Inform Current EPA Assessment Approach**

NRC = National Research Council; EPA = Environmental Protection Agency; HC = Health Canada; EFSA = European Food Safety Agency; NTP = National Toxicology Program.

## 2.3. Key Science Issues

This section identifies key areas of scientific complexity, outlining important scientific questions or areas of uncertainty for fluoride that will need to be considered in EPA's toxicity assessment. The identified key science issues pertain to evaluating the fluoride exposure measurements and interpreting health outcomes.

Based on the preliminary literature survey (Section 4) and critical review of previous reports, EPA has identified the following key scientific issues that warrant evaluation during this assessment:

- **Validity of exposure metrics in epidemiology studies**. Exposure to fluoride can be estimated using a variety of methods, such as external measures (e.g., drinking water concentrations) or internal measures (e.g., concentrations in urine, serum, or other biological matrices). Strong correlations have been reported between concentrations of fluoride in urine and drinking water (Pearson correlation coefficient, $r_p = 0.79$) and between serum and drinking water ($r_p = 0.62$) across populations (EFSA Scientific Committee, 2025). For the purpose of this assessment, EPA will consider both drinking water and internal biomarker measures to be potentially valid approaches of characterizing fluoride human exposure, but strengths and limitations of the exposure metrics will be considered during study

evaluation. For all exposure measures, a primary consideration is the analytical methodology; for example, measurement of fluoride in drinking water or urine can be accomplished with multiple laboratory techniques with varying sensitivity, specificity and susceptibility to interferences. Assessment of the analytic technique and subsequent potential for exposure measurement error will be considered during study evaluation. Additionally, the timing of exposure measurement should coincide with the critical window of exposure for a given health endpoint. Measurements of fluoride in urine or other tissues are subject to within- and between-person variability due to factors including changing exposure over the lifetime, and inter-individual differences in fluoride elimination. Thus, study evaluation will also consider whether the reported exposure biomarkers can be used to estimate oral intake in an etiologically relevant time period, based on knowledge of fluoride pharmacokinetics and lifestage sensitivities. Criteria for the consideration of exposure metrics during study evaluation will be presented in the assessment protocol.

- **Completeness of exposure characterization in epidemiology studies.** As noted above, epidemiology studies that meet the evaluation criteria may also characterize fluoride exposure using measurements in drinking water and/or biomarkers. Each of these methods for characterizing exposure has strengths and limitations. While fluoride concentration in drinking water can be an accurate and direct measure of exposure, it only provides an estimate of a single exposure source and often requires assumptions about water intake, which can be a source of measurement error. Furthermore, to extrapolate an RfD from a study that only measures fluoride in drinking water, additional steps are necessary to account for other sources of fluoride exposure. EPA notes that the study by Dean (1942) previously used to derive toxicity reference values for fluoride (Table 2-1) was conducted at a time before fluoride was added to dental products, so oral fluoride exposure in children occurred exclusively through drinking water and (to a lesser extent) food intake. This lessens concern for exposure misclassification compared with more recent studies that use drinking water as the exposure metric but are conducted in time periods where significant exposure from dental products may contribute to total intake. This is considered a strength of the Dean (1942) study. For epidemiology studies conducted after the 1940's that evaluate outcomes only in relation to fluoride concentrations in drinking water, RfD derivation will need to account for fluoride exposure from dental products such as toothpaste. As an alternative to drinking water measurements, measurements of fluoride in urine (Rango et al., 2017) or tissues, such as bone (Rugg-Gunn et al., 2011), teeth (Vieira et al., 2005), or nail clippings (Elekdag-Turk et al., 2019; Rango et al., 2017), are biomarkers of a person's total fluoride intake (Lavalle-Carrasco et al., 2021), accounting for exposure across all possible sources of fluoride (e.g., drinking water, diet, dental treatments). However, these biomarkers have limitations as well. Fluoride in blood or urine may be highly influenced by recent exposure rather than the typical or average exposure of an individual. Bone fluoride measurement is highly invasive and rare in children and pregnant women, the populations at greatest hazard from fluoride exposure. Fluoride measurement in teeth may be highly influenced by topical exposure to dental products and may not reflect systemic fluoride or total fluoride exposure. Additionally, nail clippings represent average systemic concentrations over a long period of time and inter-individual differences in fingernail and toenail

fluoride uptake can substantially influence these measurements. These biomarkers will be evaluated against other metrics of exposure for their ability to support estimation of oral intake relevant for RfD derivation.

- **Understanding the pharmacokinetics of fluoride in the body.** EPA is developing a robust pharmacokinetic (PK) analysis to aid in addressing the science issues above. The goal of the PK analysis is to link fluoride exposure to the levels within the body (Tan et al., 2020) following a comprehensive review of the absorption, distribution, metabolism, and excretion (ADME) of fluoride. PK models are the preferred method to relate external and internal measures of exposure, which is necessary to derive a reference dose based on internal dose points of departure derived from toxicity, epidemiology, or clinical studies (U.S. EPA, 2006). PK models are also a preferred approach to evaluate variability and sensitivity within a population (U.S. EPA, 2014), such as lifestage specific changes in ADME, and are routinely used in EPA toxicity assessments (U.S. EPA, 2024a, b). Some key features of fluoride ADME are that the fluoride ion is known to preferentially distribute to bone in an age-dependent manner (Richards et al., 1994), does not undergo further (Institute of Medicine, 1997) biotransformation through metabolism in the body, and is mainly excreted in the urine (Institute of Medicine, 1997). Currently, EPA is aware of two physiologically based pharmacokinetic (PBPK) models (Jean et al., 2018; Rao et al., 1995) developed to predict internal fluoride dosimetry while accounting for bone uptake and renal clearance. EPA will consider these PBPK models as well as other pharmacokinetic approaches identified through systematic review or public comment to support RfD derivation, including the approach used by EFSA (EFSA Scientific Committee, 2025). PK approaches will be evaluated based on the fit to *in vivo* human data, the accuracy of the biological and mechanistic basis for the model, and the suitability for the model to address the risk assessment context for fluoride (specifically, whether lifestage specific features of ADME are accurately described).
- **Adversity of dental fluorosis.** Dental fluorosis has been widely studied and has been commonly selected as the critical effect for the derivation of fluoride toxicity values in prior final health assessments (Table 2-1), but there is lack of consensus on how to characterize the adversity of this outcome. It is generally categorized as *mild, moderate,* or *severe*. NRC (2006) concluded that *severe* dental fluorosis (characterized by dark yellow to brown staining and pitting) should be considered adverse as it constitutes enamel loss, whereas *mild/moderate* fluorosis is primarily an aesthetic concern. The U.S. EPA (2010a) dose-response analysis was therefore based on the occurrence of *severe* dental fluorosis. In contrast, EFSA (EFSA Scientific Committee, 2025) and Health Canada (Taher et al., 2024) consider *moderate* dental fluorosis to be adverse, and the EFSA (EFSA Scientific Committee, 2025) dose-response analysis was based on the combined incidence of all severity levels, *mild* to *severe*, of dental fluorosis. EPA will consider the adversity of different stages of dental fluorosis when selecting appropriate benchmark response (BMR) values for dose-response analysis and when identifying an overall RfD for fluoride.

# 3. Overall Toxicity Assessment Objective and Specific Aims

This section outlines the overall objective and specific aims of the new fluoride toxicity assessment, including the process that EPA used to identify studies for the preliminary literature survey (Section 4). The overall objective of the new fluoride toxicity assessment is to develop an RfD for oral fluoride exposure. This will be accomplished through specific aims, which are listed below:

- Conduct a comprehensive literature search to identify epidemiological studies evaluating neurodevelopmental toxicity or dental fluorosis following fluoride exposure.
- Extract study design information for studies meeting the inclusion criteria to develop literature inventories that characterize the extent of the evidence for a topic, called a systematic evidence map (SEM).
- Identify studies reporting pharmacokinetic information or PBPK models for fluoride in humans, which may be used to inform the dose-response analysis.
- Conduct evaluations of individual epidemiological studies that meet the inclusion criteria (Table 4-1 and defined in Section 4.1) and that report results with sufficient quantitative detail to conduct dose-response modeling (e.g., regression coefficients presented with statistical measure of variation). The evaluations of each individual study will consider factors which might impact the strength or direction of the observed effects (i.e., potential risk of bias) and factors that limit the ability of a study to detect an association when one exists (i.e., sensitivity).
- Conduct scientific and technical review of PBPK models. A fluoride PBPK model will be integrated with the dose-response analysis to determine total exposure from limited environmental and biological measurements (e.g., drinking water and urine concentrations).
- Select relevant epidemiology studies for dose-response modeling based on study evaluation conclusions and consideration of dose-response suitability criteria. Extract data on relevant health outcomes from the selected studies.
- Derive an RfD from the available robust epidemiological data.
- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence, limitations of the systematic review, and consideration of dose relevance and pharmacokinetic information. Identification of key data gaps will be explicitly addressed as part of characterizing the database uncertainty factor ($UF_D$). Uncertainty factors will be considered and set during toxicity assessment development.

This assessment is using systematic review methods, consistent with Gold Standard Science, to identify and evaluate the relevant health effects literature for fluoride. A summary of the literature selection process for the systematic review is provided in Figure 3-1. The assessment will be conducted according to standard operating procedures (U.S. EPA, 2022), and a Systematic Review Protocol will be finalized after considering the public comments received on this Preliminary Assessment Plan and Literature Survey.

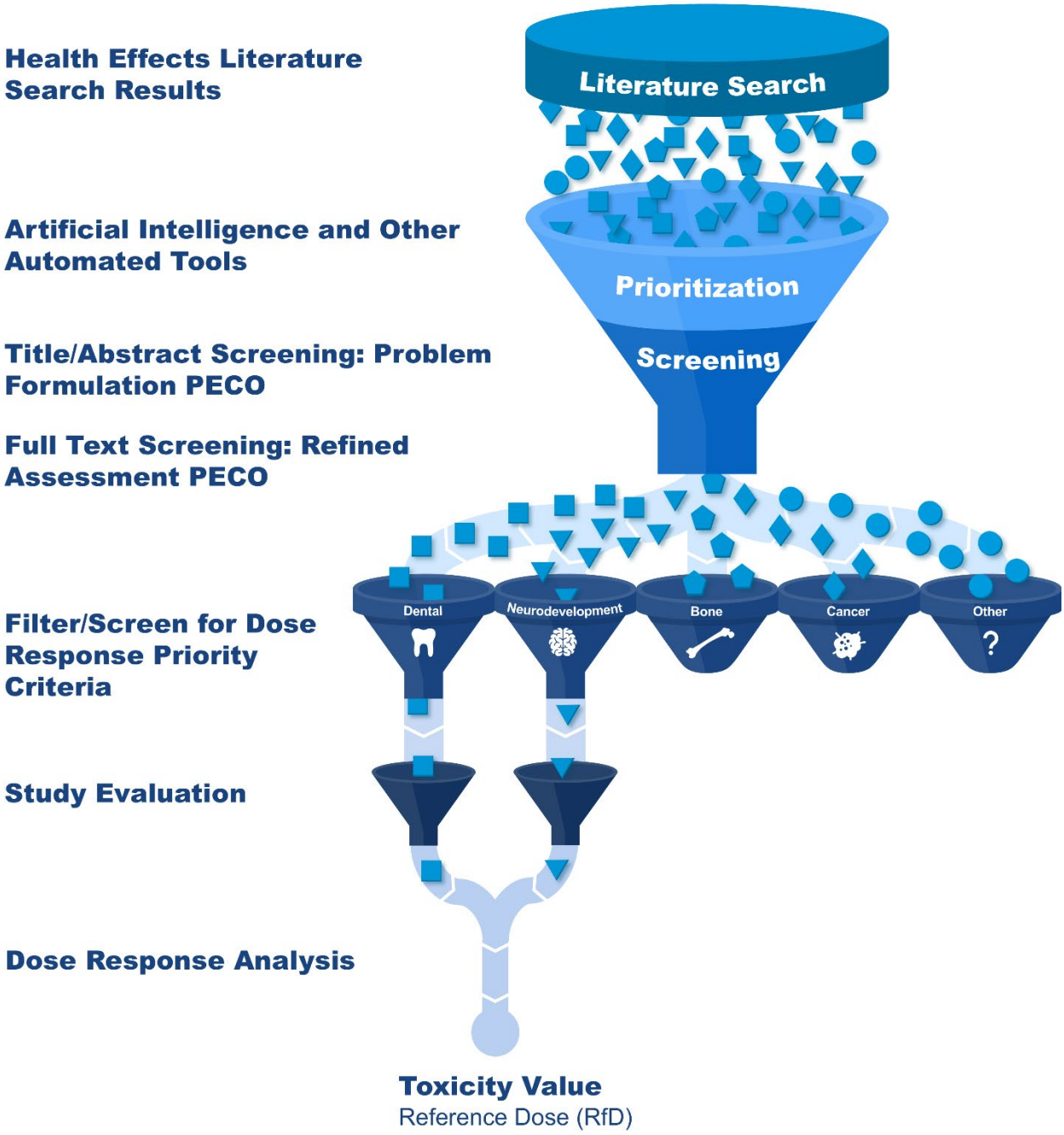


**Figure 3-1. Summary of Assessment Literature Selection Process**

PECO = populations, exposures, comparators, and outcomes; RfD = reference dose.

# 4. Preliminary Literature Survey

This section describes the methods and results of the systematic literature search and screening to identify the best available science on human health effects after fluoride exposure. EPA identified 562 relevant studies that have been prioritized for subsequent systematic review steps.

## 4.1. Literature Search and Screening Methods

To identify relevant studies on fluoride for the preliminary literature survey, EPA performed a literature search and screening using systematic review methods. Methods are briefly summarized here and described in detail in Appendix B.

Briefly, peer-reviewed studies were identified by searching scientific databases that include human health toxicity studies. Additional studies were identified through review of citations in published reports from EPA and other health agencies. Studies identified in the literature search then underwent prioritization using AI and other automated tools (Appendix B.2.2) to efficiently identify studies most likely to be relevant. Prioritized studies were then screened according to specific criteria for the fluoride toxicity assessment, also called the populations, exposures, comparators, and outcomes (PECO) criteria, which are a set of prespecified characteristics in these four categories used to identify studies that are relevant to the specific aims. This was done in three phases:

- Studies were first screened at the title-abstract level (Appendix B.2.3) by multiple independent reviewers according to an initial problem formulation PECO (Table B-2), which was broad and included all health outcomes in both humans and experimental animal models.
- Studies meeting the initial problem formulation PECO then underwent an additional prioritization step to identify studies that evaluated dental or neurological effects (i.e., the most sensitive children's health outcomes that are the focus of the new assessment) or cancer (to develop the cancer literature inventory; Appendix C). This was accomplished by cross-referencing the citations in published reports and by using health outcome filters in Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT) Review software (described in Appendix B.2.4).
- The prioritized studies were then screened at the full-text level (i.e., the entire article) according to a refined assessment PECO (Table 4-1), which is narrower in scope, to identify epidemiological studies reporting developmental neurotoxicity or dental fluorosis after fluoride exposure due to the assessment scope (Section 2).

In addition to studies that meet the PECO criteria and studies excluded as not relevant to the assessment, studies containing supplemental material that are also potentially relevant to the specific aims were inventoried during the literature screening process. Table 4-2 presents the major categories of supplemental material. Supplemental studies could emerge as being critically important to the assessment and may need to be evaluated and summarized at the individual study level (e.g., ADME or PK studies), or might be helpful to provide context, or might not be cited at all in the assessment.

**Table 4-1. Refined Populations, Exposures, Comparators, and Outcomes Criteria for the Fluoride Assessment[a]**

| PECO Element | Evidence |
|---|---|
| Populations | Human: Any population and lifestage. |
| Exposures | Relevant forms: Any exposure to fluoride, and/or related forms (see list in Problem Formulation PECO).<br>Human: Any exposure to the chemicals listed above via oral routes or unknown/multiple routes (e.g., biomonitoring studies) occurring during lifestages ranging from the fetus through adolescence. Other exposure routes, including inhalation or dermal, will be excluded and tagged as supplemental. |
| Comparators | Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of the chemical or interest, or exposure to the chemical of interest for shorter periods of time. Case reports and case series will be excluded and tagged as supplemental if other PECO parameters are met. |
| Outcomes | Human: Dental fluorosis and neurodevelopmental outcomes (including but not limited to cognition, motor, and behavior). Studies of dental caries alone without additional priority outcomes will not be included as they are primarily assessing beneficial effects of exposure. |
| PBPK Models | Studies describing PK or PBPK models will be included (see Problem Formulation PECO for details). |

PECO = populations, exposures, comparators, and outcomes; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetic.

[a] The refined PECO criteria for the Fluoride Assessment will be used to identify studies for study evaluation and dose-response analysis.

**Table 4-2. Categories of Potentially Relevant Supplemental Material for the Fluoride Assessment**

| Category | Evidence |
|---|---|
| Mechanistic studies | Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian (genotoxicity) model systems, including *in vitro*, *in vivo* (by various routes of exposure), *ex vivo*, and *in silico* studies. |
| Beneficial-only health outcome | Studies reporting only the beneficial effects of fluoride treatment or exposure without quantitatively reporting adverse effects or side effects. Beneficial is defined based on the intent of the study (e.g., was the study designed to assess the use of fluoride to prevent cavities). Studies reporting an adverse outcome with a potentially beneficial response (e.g., observational study reporting reduced risk of cancer) will not be considered beneficial-only studies and will be included as PECO relevant. |
| Non-mammalian model systems | Studies in non-mammalian model systems (e.g., fish, birds, *C. elegans*). |
| ADME and PK | Studies designed to capture information regarding ADME, including PK studies. Such information may be helpful in updating or revising the parameters used in existing PBPK models. |
| Acute/short-term duration exposures | Animal studies of fewer than 28 days (unless the study is a developmental and reproductive health outcome study). |
| Only one exposure group | Animal studies with only one exposure group (e.g., control and 1 mg/kg/day fluoride). |
| Non-oral routes of exposure | Studies addressing routes of exposure that fall outside the PECO scope, include inhalation and dermal exposure routes. |
| Exposure characteristics (no health outcome) | Exposure characteristic studies include data that are unrelated to toxicological endpoints, but which provide information on exposure sources or measurement properties of the environmental agent (e.g., demonstrate a biomarker of exposure). |
| Susceptible populations (no health outcome) | Studies that identify potentially susceptible subgroups (e.g., studies that focus on a specific demographic, lifestage, or genotype). |
| Environmental fate or occurrence (including food) | Studies that focus on describing where the chemical will end up after it is used and released into the environment. |
| Mixture studies | Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. |
| Case studies or case series | Case reports and case series will be tracked as potentially relevant supplemental information if other PECO parameters are met. |

PECO = populations, exposures, comparators, and outcomes; ADME = absorption, distribution, metabolism, and excretion; PK = pharmacokinetic; PBPK = physiologically based pharmacokinetic.

## 4.2. Literature Survey Results

Using methods summarized in Section 4.1 (details in Appendix B), 268,967 unique references[2] were identified from performing the systematic literature search. The numbers reported in the following sections represent the systematic review steps performed to date and are current as of January 12, 2026; EPA continues to screen at the full-text level to identify all studies that meet the refined PECO criteria.[3] These studies underwent prioritization using a combination of methods including AI and other automated tools, which reduced the number of studies for screening to 74,102 prioritized studies. EPA further narrowed these prioritized studies through title-abstract screening, additional prioritization for dental and neurodevelopmental outcomes, and full-text screening which identified 562 studies that met EPA's inclusion criteria (i.e., the refined PECO criteria described in Table 4-1). Study design details were extracted for these studies to develop an SEM, which characterizes the amount and type of information available for the two priority children's health effects, dental fluorosis and developmental neurotoxicity. Figure 4-1 provides a summary of the available studies for each health system based on the type and timing of exposure while Figure 4-2 summarizes the available studies for each health system based on study type.

User-friendly, publicly available applications are available on the internet to visualize and explore the preliminary literature survey results. First, an interactive literature flow diagram illustrates how studies are included and excluded at each step of the screening process. These results are available in Appendix D, Figure D-1 with the interactive version available at: https://public.tableau.com/app/profile/ow.hecd.visuals/viz/LiteratureSurveyforPreliminaryFluorideAssessmentPlan/LitFlow.

Additionally, the 562 studies that met the literature survey inclusion criteria are summarized in an interactive literature dashboard (available at: https://public.tableau.com/app/profile/ow.hecd.visuals/viz/FluorideEpidemiologyEvidenceMap/ReadMe). This dashboard is a web-based application that allows the user to display the SEM by various study aspects (e.g., study design, health system, exposure measure, lifestage at exposure measurement, an initial determination of whether the study presents sufficient data to be used for dose-response analysis, and year of publication). Figure 4-3 provides an example of the interactive literature dashboard filtered for a specific lifestage. The full or filtered list of studies containing all study details can be downloaded directly from this web-based application. Links to each reference in the Health and Environmental Research Online (HERO) database are publicly available.

Of the 562 studies, a total of 489 studies examined dental fluorosis and 98 studies examined neurodevelopmental outcomes, including cognitive, behavioral, and sensory/motor effects. The majority of human epidemiology prioritized studies are cross-sectional (n = 455), followed by cohorts (n = 56) and case-control studies (n = 32). Most studies measured fluoride exposure in drinking water (n = 441) or using biomarkers (n = 134), primarily urine. Other methods to characterize fluoride exposure included questionnaires, total intake, dental sources, and endemic

[2] Total references (268,967) reflects 268,647 identified through database searches and 320 identified from other sources.
[3] As of January 12, 2026, 296 studies are awaiting or currently under review at the full-text level.

fluorosis. For dental fluorosis, most studies measured exposure at the population level (n = 358) vs. individual level (n = 222), while for neurodevelopment, more studies measured exposure at the individual level (n = 63 vs. 57) (some studies provided measures of exposure at both levels). Most studies lacked sufficient data to be used for dose-response analysis (n = 436), while the remainder will be assessed further for suitability (n = 127).

| Exposure Measure | Timing of Exposure Measurement | Health System | | Total Distinct References |
|---|---|---|---|---|
| | | Dental | Neurodevelopmental | |
| Biomonitoring | In utero | | 15 | 15 |
| | At birth | 1 | 2 | 3 |
| | Early childhood (<6 years) | 24 | 11 | 32 |
| | Late childhood (6–<11 years) | 76 | 39 | 103 |
| | Adolescence (11–<21 years) | 73 | 35 | 99 |
| Drinking water | In utero | 6 | 4 | 10 |
| | At birth | 21 | 6 | 26 |
| | Early childhood (<6 years) | 140 | 14 | 151 |
| | Late childhood (6–<11 years) | 304 | 51 | 337 |
| | Adolescence (11–<21 years) | 303 | 40 | 330 |
| Other | In utero | 5 | 4 | 9 |
| | At birth | 13 | 2 | 15 |
| | Early childhood (<6 years) | 80 | 10 | 87 |
| | Late childhood (6–<11 years) | 131 | 15 | 140 |
| | Adolescence (11–<21 years) | 114 | 13 | 122 |
| **Total Distinct References** | | 489 | 98 | 562 |

**Figure 4-1. Survey of Human Studies that Met Refined Populations, Exposures, Comparators, and Outcomes Criteria with Type and Timing of Exposure Measure by Health System**

The numbers indicate the number of studies that investigated a particular topic, not the number of studies that observed an association with fluoride exposure. If a study evaluated multiple health outcomes or lifestages of exposure, it is shown here multiple times.

| Study Design | Exposure Measure | Health System: Dental | Health System: Neurodevelopmental | Total Distinct References |
|---|---|---|---|---|
| Case-control | Biomonitoring | 11 | 2 | 13 |
| | Drinking water | 16 | 1 | 17 |
| | Other | 17 | 1 | 18 |
| Cohort | Biomonitoring | 2 | 14 | 16 |
| | Drinking water | 20 | 6 | 25 |
| | Other | 25 | 7 | 32 |
| Controlled trial | Drinking water | 3 | | 3 |
| | Other | 9 | | 9 |
| Cross-sectional | Biomonitoring | 74 | 46 | 108 |
| | Drinking water | 349 | 59 | 389 |
| | Other | 131 | 14 | 139 |
| Ecological | Drinking water | 12 | | 12 |
| | Other | 7 | 1 | 8 |
| Other | Biomonitoring | 2 | | 2 |
| | Drinking water | 4 | | 4 |
| **Total Distinct References** | | 489 | 98 | 562 |

**Figure 4-2. Survey of Human Studies That Met Refined Populations, Exposures, Comparators, and Outcomes Criteria with Study Design and Type of Exposure Measure by Health System**

The numbers indicate the number of studies that investigated a particular topic, not the number of studies that observed an association with fluoride exposure. If a study evaluated multiple health outcomes, study designs, or exposure metrics, it is shown here multiple times.

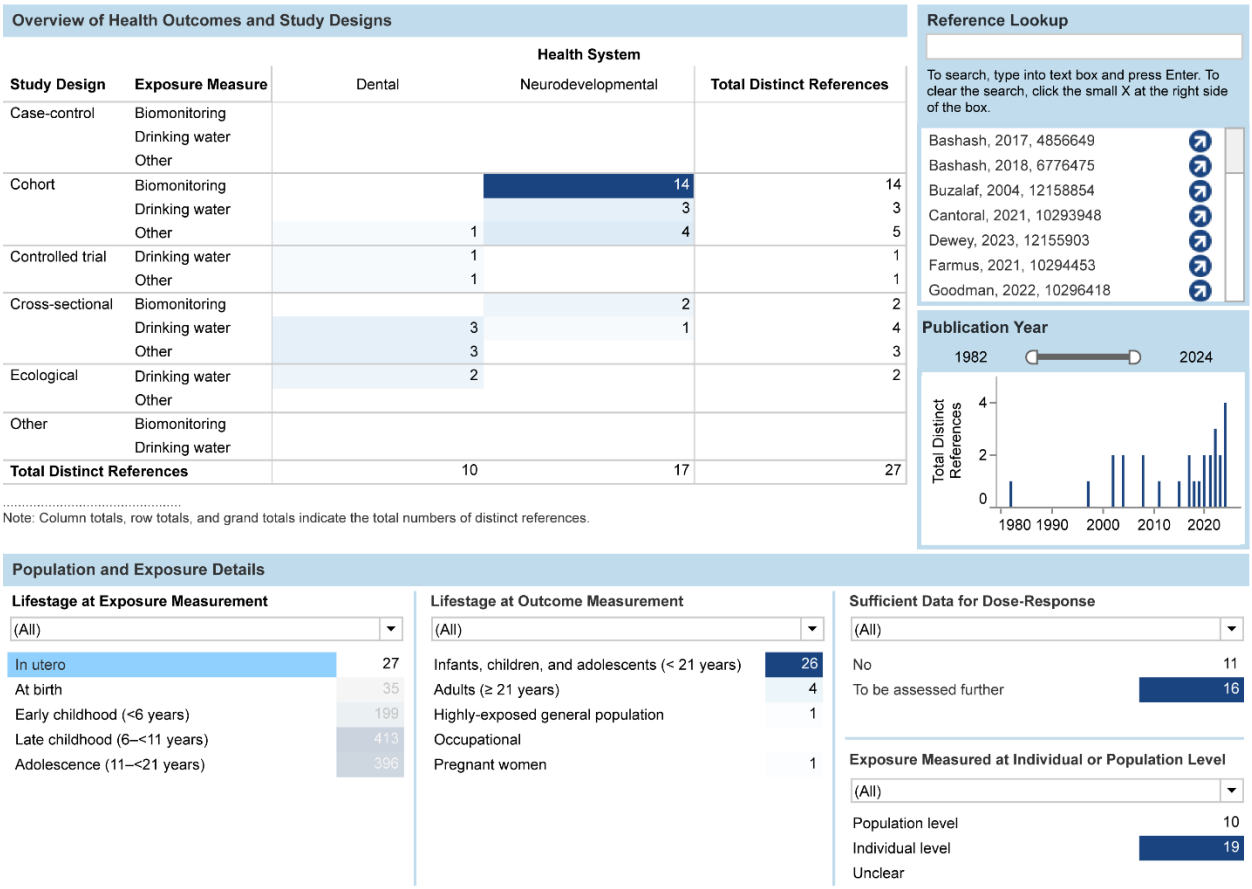


**Figure 4-3. Interactive Literature Dashboard Example Output: Populations, Exposures, Comparators, and Outcomes-relevant Studies Filtered for "In Utero" Lifestage of Exposure**

# 5. Next Steps

Publication of the Preliminary Assessment Plan and Literature Survey is the first step in developing a new human health toxicity assessment on fluoride in drinking water based on gold standard science. Following closure of the public comment period on this Preliminary Assessment Plan and Literature Survey document, EPA will review comments received and incorporate feedback, as appropriate, into the scoping and problem formulation as the Agency begins developing a Systematic Review Protocol. The Systematic Review Protocol will describe in detail how EPA will conduct the toxicity assessment, including specific methods and approaches to do the following:

- Develop fluoride-specific study evaluation considerations to transparently and consistently review each relevant human study;
- Identify the most sensitive health effect(s) after fluoride exposure;
- Identify studies best-suited to determine what fluoride exposure levels result in harmful human health effects;
- Conduct dose-response on the best available studies, incorporating approaches to estimate total human fluoride exposure; and
- Derive an RfD for fluoride following selection of uncertainty factors.

EPA will follow the Systematic Review Protocol to develop a draft Fluoride Human Health Toxicity Assessment. The draft Assessment will:

- Follow EPA human health risk assessment methods and guidance;
- Summarize the health effects associated with exposure to fluoride based on the best available science;
- Identify the most sensitive health effect(s) in children; and
- Identify the fluoride levels that a person can be exposed to and be unlikely to experience harmful health effects.

EPA will release the draft Fluoride Human Health Toxicity Assessment for external peer review and public comment. Following completion of the peer review process and closure of public comment period, EPA will review and consider comments received and revise the assessment accordingly.

EPA will then publish a final Fluoride Human Health Toxicity Assessment, which will serve as an updated scientific foundation that can inform future steps under SDWA. Throughout the assessment's development, EPA will rely on gold standard science and follow a systematic review process to evaluate the best available science on the health effects of fluoride.

# 6. References

Acharya, S. (2005). Dental caries, its surface susceptibility and dental fluorosis in South India. Int Dent J 55: 359-364.

American Dental Association. (2025). Letter to the EPA administrator. Washington, DC. https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/advocacy/regulatory-reform/letter_epa_administrator_priorities.pdf

ATSDR (Agency for Toxic Substances and Disease Registry). (2003). Toxicological profile for fluorides, hydrogen fluoride, and fluorine [ATSDR Tox Profile]. (NTIS PB2004-100002). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Barberio, AM; Hosein, FS; Quiñonez, C; McLaren, L. (2017a). Fluoride exposure and indicators of thyroid functioning in the Canadian population: implications for community water fluoridation. J Epidemiol Community Health 71: 1019-1025.

Barberio, AM; Quiñonez, C; Hosein, FS; McLaren, L. (2017b). Fluoride exposure and reported learning disability diagnosis among Canadian children: Implications for community water fluoridation. Can J Public Health 108: e229-e239.

Bartos, M; Gumilar, F; Gallegos, CE; Bras, C; Dominguez, S; Cancela, LM; Minetti, A. (2019). Effects of perinatal fluoride exposure on short- and long-term memory, brain antioxidant status, and glutamate metabolism of young rat pups. Int J Toxicol 38: 405-414.

Bartos, M; Gumilar, F; Gallegos, CE; Bras, C; Dominguez, S; Mónaco, N; Esandi, MDC; Bouzat, C; Cancela, LM; Minetti, A. (2018). Alterations in the memory of rat offspring exposed to low levels of fluoride during gestation and lactation: Involvement of the α7 nicotinic receptor and oxidative stress. Reprod Toxicol 81: 108-114.

Bashash, M; Thomas, D; Hu, H; Martinez-Mier, EA; Sanchez, BN; Basu, N; Peterson, KE; Ettinger, AS; Wright, R; Zhang, Z; Liu, Y; Schnaas, L; Mercado-García, A; Téllez-Rojo, MM; Hernández-Avila, M. (2017). Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in mexico. Environ Health Perspect 125: 097017.

Bassin, EB; Wypij, D; Davis, RB; Mittleman, MA. (2006). Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes & Control 17: 421-428. https://doi.org/10.1007/s10552-005-0500-6

Bataineh, HN; Nusier, MK. (2006). Impact of 12-week ingestion of sodium fluoride on aggression, sexual behavior, and fertility in adult male rats. Fluoride 39: 293-301.

Bera, I; Sabatini, R; Auteri, P; Flace, P; Sisto, G; Montagnani, M; Potenza, MA; Marasciulo, FL; Carratu, MR; Coluccia, A; Borracci, P; Tarullo, A; Cagiano, R. (2007). Neurofunctional effects of developmental sodium fluoride exposure in rats. Eur Rev Med Pharmacol Sci 11: 211-224.

CDC (U.S. Centers for Disease Control and Prevention). (2024). About community water fluoridation. Available online at https://www.cdc.gov/fluoridation/about/index.html#:~:text=Community%20water%20fluoridation%20is%20a,level%20proven%20to%20prevent%20cavities (accessed 01/09/2026).

Charugundla, BR; Anjum, S; Mocherla, M. (2015). Comparative effect of fluoride, essential oil and chlorhexidine mouth rinses on dental plaque and gingivitis in patients with and without dental caries: A randomized controlled trial. Int J Dent Hyg 13: 104-109.

Comber, H; Deady, S; Montgomery, E; Gavin, A. (2011). Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. Cancer Causes Control 22: 919-924.

Das, TK; Susheela, AK; Gupta, IP; Dasarathy, S; Tandon, RK. (1994). Toxic effects of chronic fluoride ingestion on the upper gastrointestinal tract. J Clin Gastroenterol 18: 194-199.

Dean, HT. (1942). The investigation of physiological effects of the epidemiological method. American Association for the Advancement of Science23-31.

EFSA Scientific Committee. (2025). Updated consumer risk assessment of fluoride in food and drinking water including the contribution from other sources of oral exposure. EFSA journal, 23: e9478. https://doi.org/10.2903/j.efsa.2025.9478

Elekdag-Turk, SA-O; Almuzian, M; Turk, T; Buzalaf, MAR; Alnuaimi, A; Dalci, O; Darendeliler, MA. (2019). Big toenail and hair samples as biomarkers for fluoride exposure - a pilot study. BMC Oral Health 19: 82.

Erickson, JD. (1980). Down syndrome, water fluoridation, and maternal age. Teratology 21: 177-180.

Erickson, JD; Oakley, GP, Jr.; Flynt, JW, Jr.; Hay, S. (1976). Water fluoridation and congenital malformations: No association. J Am Dent Assoc 93: 981-984.

Ershow, AB; Cantor, KP. (1989). Total water and tapwater intake in the united states: Population-based estimates of quantities and sources. Bethesda, MD: Life Sciences Research Office.

Green, R; Lanphear, B; Hornung, R; Flora, D; Martinez-Mier, EA; Neufeld, R; Ayotte, P; Muckle, G; Till, C. (2019). Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. JAMA Pediatr 173: 940-948.

Health Canada. (2010). Guidelines for Canadian drinking water quality: Guideline technical document – fluoride. (ISBN 978-1-100-18261-2). Ottawa, Ontario: Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Health Canada. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-fluoride.html

Health Canada. (2024). Expert panel meeting on the health effects of fluoride in drinking water: summary report, June 8-9, 2023. Ottawa, ON: Health Canada. https://publications.gc.ca/site/eng/9.933047/publication.html

Heindel, JJ; Bates, HK; Price, CJ; Marr, MC; Myers, CB; Schwetz, BA. (1996). Developmental toxicity evaluation of sodium fluoride administered to rats and rabbits in drinking water. Fundam Appl Toxicol 30: 162-177.

Hodge, HC. (1950). The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. J Am Dent Assoc 40: 436-439.

Howard, BE; Phillips, J; Tandon, A; Maharana, A; Elmore, R; Mav, D; Sedykh, A; Thayer, K; Merrick, BA; Walker, V; Rooney, A; Shah, RR. (2020). SWIFT-active screener: Accelerated document screening through active learning and integrated recall estimation. Environ Int 138: 105623.

Huang, X; Chen, K; Wang, C; Gao, P. (2025). Characteristics of fluoride adsorption in different soil types: Potential factors and implications for environmental risk assessment. Environmental Pollution 367: 125537.

IARC (International Agency for Research on Cancer). (1987a). Fluorides. Environmental health criteria 227. World Health Organization. https://www.inchem.org/documents/ehc/ehc/ehc227.htm

IARC (International Agency for Research on Cancer). (1987b). Summaries & evaluations. Fluorides (inorganic, used in drinking-water) (pp. 208). World Health Organization. https://www.inchem.org/documents/iarc/suppl7/fluorides.html

Institute of Medicine. (1997). Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: The National Academies Press. https://nap.nationalacademies.org/catalog/5776/dietary-reference-intakes-for-calcium-phosphorus-magnesium-vitamin-d-and-fluoride

Jacqmin, H; Commenges, D; Letenneur, L; Barberger-Gateau, P; Dartigues, JF. (1994). Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 139: 48-57.

Jean, KJ; Wassef, N; Gagnon, F; Valcke, M. (2018). A physiologically-based pharmacokinetic modeling approach using biomonitoring data in order to assess the contribution of drinking water for the achievement of an optimal fluoride dose for dental health in children. International Journal of Environmental Research and Public Health 15. https://heronetnext.epa.gov/api/reference/document/827044/download

Kampouri, M; Gustin, K; Stråvik, M; Barman, M; Sandin, A; Sandberg, AS; Wold, AE; Vahter, M; Kippler, M. (2023). Associations of gestational and early-life exposure to toxic metals and fluoride with a diagnosis of food allergy or atopic eczema at 1 year of age. Environ Int 178: 108071.

Khandare, AL; Validandi, V; Gourineni, SR; Gopalan, V; Nagalla, B. (2018). Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study. Environ Monit Assess 190: 110.

Kivrak, Y; Kars, T. (2012). Effects of fluoride on anxiety and depression in mice [Research report] (pp. 302-306). https://fluoridealert.org/wp-content/uploads/kivrak-20121.pdf

Kumar, JV; Swango, PA. (1999). Fluoride exposure and dental fluorosis in Newburgh and Kingston, New York: Policy implications. Community Dent Oral Epidemiol 27: 171-180.

Lavalle-Carrasco, J; Molina-Frechero, N; Nevárez-Rascón, M; Sánchez-Pérez, L; Hamdan-Partida, A; González-González, R; Cassi, D; Isiordia-Espinoza, MA; Bologna-Molina, R. (2021). Recent biomarkers for monitoring the systemic fluoride levels in exposed populations: A systematic review. International Journal of Environmental Research and Public Health.

Lee, WS; Kim, JH; Han, B; Lee, GC; Jung, HR; Shin, YJ; Ha, EK; Lee, E; Lee, S; Han, MY. (2024). Association of fluoride exposure with disease burden and neurodevelopment outcomes in children in South Korea. World J Pediatr 20: 1029-1042.

Levy, M; Leclerc, BS. (2012). Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents. Cancer Epidemiol 36: e83-88.

Li, M; Cui, J; Gao, Y; Zhang, W; Sun, L; Liu, X; Liu, Y; Sun, D. (2015). Pathological changes and effect on the learning and memory ability in rats exposed to fluoride and aluminum. Toxicology Research 4: 1366-1373. https://doi.org/10.1039/c5tx00050e

Li, Y; Liang, C; Slemenda, CW; Ji, R; Sun, S; Cao, J; Emsley, CL; Ma, F; Wu, Y; Ying, P; Zhang, Y; Gao, S; Zhang, W; Katz, BP; Niu, S; Cao, S; Johnston, CC. (2001a). Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. J Bone Miner Res 16: 932-939. http://dx.doi.org/10.1359/jbmr.2001.16.5.932

Li, Y; Liang, C; Slemenda, CW; Ji, R; Sun, S; Cao, J; Emsley, CL; Ma, F; Wu, Y; Ying, P; Zhang, Y; Gao, S; Zhang, W; Katz, BP; Niu, S; Cao, S; Johnston, CC, Jr. (2001b). Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. J Bone Miner Res 16: 932-939.

Liu, Y; Téllez-Rojo, M; Hu, H; Sánchez, BN; Martinez-Mier, EA; Basu, N; Mercado-García, A; Solano-González, M; Peterson, KE. (2019). Fluoride exposure and pubertal development in children living in Mexico City. Environ Health 18: 26.

Lu, Y; Luo, Q; Cui, H; Deng, H; Kuang, P; Liu, H; Fang, J; Zuo, Z; Deng, J; Li, Y; Wang, X; Zhao, L. (2017). Sodium fluoride causes oxidative stress and apoptosis in the mouse liver. Aging 9: 1623-1639.

Make America Healthy Again Commission. (2025). Make our children healthy again strategy. https://www.whitehouse.gov/wp-content/uploads/2025/09/The-MAHA-Strategy-WH.pdf (accessed 01/12/2026).

Mascarenhas, AK; Burt, BA. (1998). Fluorosis risk from early exposure to fluoride toothpaste. Community Dent Oral Epidemiol 26: 241-248.

Maurer, JK; Cheng, MC; Boysen, BG; Anderson, RL. (1990). Two-year carcinogenicity study of sodium fluoride in rats. J Natl Cancer Inst 82: 1118-1126.

Maurer, JK; Cheng, MC; Boysen, BG; Squire, RA; Strandberg, JD; Weisbrode, SE; Seymour, JL; Anderson, RL. (1993). Confounded carcinogenicity study of sodium fluoride in CD-1 mice. Regul Toxicol Pharmacol 18: 154-168.

McClure, FJ. (1943). Ingestion of fluoride and dental caries: Quantitative relations based on food and water requirements of children 1-12 years old. Am J Dis Child 66: 362-369. http://dx.doi.org/10.1001/archpedi.1943.02010220015002

NIH (National Institutes of Health). (2025). Fluoride fact sheet for health professionals. Available online at https://ods.od.nih.gov/factsheets/Fluoride-HealthProfessional/ (accessed 01/09/2026).

Niu, R; Han, H; Zhang, Y; Wang, J; Zhang, J; Yin, W; Yin, X; Sun, Z; Wang, J. (2016). Changes in liver antioxidant status of offspring mice induced by maternal fluoride exposure during gestation and lactation. Biol Trace Elem Res 172: 172-178.

NRC (National Research Council). (1993). Health effects of ingested fluoride. Washington, DC: National Academy Press. https://fluoridealert.org/wp-content/uploads/nrc.report.1993.pdf

NRC (National Research Council). (2006). Fluoride in drinking water: A scientific review of EPA's standards. Washington, DC: The National Academies Press. https://nap.nationalacademies.org/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards

NTP (National Toxicology Program). (1990). NTP toxicology and carcinogenesis studies of sodium fluoride (CAS No. 7681-49-4) in F344/N rats and B6C3F1 mice (drinking water studies). In National Toxicology Program technical report series (pp. 1-448). Research Triangle Park, NC.

NTP (National Toxicology Program). (1992). NTP supplemental 2-year study of sodium fluoride in male F344 rats (CAS No. 7681-49-4). Study No. C55221D. Research Triangle Park, NC. https://ntp.niehs.nih.gov/go/nafabs

NTP (National Toxicology Program). (2024). NTP monograph on the state of the science concerning fluoride exposure and neurodevelopment and cognition: a systematic review (pp. xviii - xix). Research Triangle Park, NC: U.S. Department of Health and Human Services. https://ntp.niehs.nih.gov/sites/default/files/2024-08/fluoride_final_508.pdf

OEHHA (Office of Environmental Health Hazard Assessment). (2008). Chronic RELs and toxicity summaries using the previous version of the hot spots risk assessment guidelines. (Appendix D.3). https://oehha.ca.gov/air/crnr/notice-adoption-air-toxics-hot-spots-program-technical-support-document-derivation-noncancer

OEHHA (Office of Environmental Health Hazard Assessment). (2011a). Carcinogen identification committee meeting scheduled for October 12 and 13, 2011. Available online at https://oehha.ca.gov/proposition-65/events/carcinogen-identification-committee-meeting-scheduled-october-12-and-13-2011 (accessed 01/09/2026).

OEHHA (Office of Environmental Health Hazard Assessment). (2011b). Evidence on the carcinogenicity of fluoride and Its salts. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Branch. https://oehha.ca.gov/sites/default/files/media/downloads/proposition-65/chemicals/fluoride070811.pdf

Pendrys, DG; Katz, RV; Morse, DE. (1996). Risk factors for enamel fluorosis in a nonfluoridated population. Am J Epidemiol 143: 808-815.

Picco, DC; Delbem, AC; Sassaki, KT; Sumida, DH; Antoniali, C. (2014). The effect of chronic treatment with fluoride on salivary activity, tooth, and bone in spontaneously hypertensive rats (SHR). Naunyn Schmiedebergs Arch Pharmacol 387: 321-328.

Rango, T; Vengosh, A; Jeuland, M; Whitford, GM; Tekle-Haimanot, R. (2017). Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population. Sci Total Environ 596-597: 1-11. https://heronetnext.epa.gov/api/reference/document/802635/download

Rao, HV; Beliles, RP; Whitford, GM; Turner, CH. (1995). A physiologically based pharmacokinetic model for fluoride uptake by bone. Regulatory Toxicology and Pharmacology 22: 30-42. https://heronetnext.epa.gov/api/reference/document/25372/download

Reddy, PS; Pushpalatha, T; Reddy, PS. (2007). Suppression of male reproduction in rats after exposure to sodium fluoride during early stages of development. Naturwissenschaften 94: 607-611.

Richards, A; Mosekilde, L; Sogaard, CH. (1994). Normal age-related-changes in fluoride content of vertebral trabecular bone – relation to bone quality. Bone 15: 21-26. https://heronetnext.epa.gov/api/reference/document/828085/download

Richards, GA; Ford, JM. (1979). Cancer mortality in selected New South Wales localities with fluoridated and non-fluoridated water supplies. Med J Aust 2: 521-523.

Riddell, JK; Malin, AJ; Flora, D; McCague, H; Till, C. (2019). Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth. Environ Int 133: 105190.

Rocha-Amador, D; Navarro, ME; Carrizales, L; Morales, R; Calderón, J. (2007). Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cad Saude Publica 23 Suppl 4: S579-587.

Rugg-Gunn, AJ; Rugg-Gunn, AJ; Enrique Villa, A; Rabelo Buzalaf, MA. (2011). Contemporary biological markers of exposure to fluoride [Review]. In Monographs in Oral Science. https://heronetnext.epa.gov/api/reference/document/828399/download

Russ, TC; Killin, LOJ; Hannah, J; Batty, GD; Deary, IJ; Starr, JM. (2020). Aluminium and fluoride in drinking water in relation to later dementia risk. Br J Psychiatry 216: 29-34.

Saha, A; Mukherjee, AK; Ravichandran, B. (2016). Musculoskeletal problems and fluoride exposure: A cross-sectional study among metal smelting workers. Toxicol Ind Health 32: 1581-1588.

Schwartz, GG. (2014). Eye cancer incidence in U.S. states and access to fluoridated water. Cancer Epidemiol Biomarkers Prev 23: 1707-1711.

Sharashenidze, M; Tkeshelashvili, V; Nanobashvili, K. (2020). Dental fluorosis prevalence, severity and associated risk factors in pre-school aged children residing in fluoride deficient regions of Georgia. Georgian Med News 306: 57-61.

Skotowski, MC; Hunt, RJ; Levy, SM. (1995). Risk factors for dental fluorosis in pediatric dental patients. J Public Health Dent 55: 154-159.

Soto-Barreras, U; Escalante-Villalobos, K; Holguín-Loya, B; Perez-Aguirre, B; Nevárez-Rascón, Z; MartÌnez-Martínez, R; Loyola-Rodríguez, J. (2019). Effect of fluoride in drinking water on dental caries and IQ in children (pp. 474-482). Chihuahua, Mexico. https://fluoridealert.org/wp-content/uploads/soto-barreras-2019.pdf

Sowanou, A; Meng, X; Zhong, N; Ma, Y; Li, A; Wang, J; Li, H; Pei, J; Gao, Y. (2022). Association between osteoarthritis and water fluoride among tongyu residents, china, 2019: A case-control of population-based study. Biol Trace Elem Res 200: 3107-3116.

Sun, Z; Li, S; Guo, Z; Li, R; Wang, J; Niu, R; Wang, J. (2018). Effects of fluoride on SOD and CAT in testis and epididymis of mice. Biol Trace Elem Res 184: 148-153.

Taher, MK; Momoli, F; Go, J; Hagiwara, S; Ramoju, S; Hu, X; Jensen, N; Terrell, R; Hemmerich, A; Krewski, D. (2024). Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water. Critical Reviews in Toxicology 54: 2-34. http://dx.doi.org/10.1080/10408444.2023.2295338

Tan, YM; Chan, M; Chukwudebe, A; Domoradzki, J; Fisher, J; Hack, CE; Hinderliter, P; Hirasawa, K; Leonard, J; Lumen, A; Paini, A; Qian, H; Ruiz, P; Wambaugh, J; Zhang, F; Embry, M. (2020). PBPK model reporting template for chemical risk assessment applications. Regulatory Toxicology and Pharmacology 115.

Taylor, KW; Eftim, SE; Sibrizzi, CA; Blain, RB; Magnuson, K; Hartman, PA; Rooney, AA; Bucher, JR. (2025). Fluoride exposure and children's IQ scores: a systematic review and meta-analysis. JAMA Pediatrics 179: 282-292. https://doi.org/10.1001/jamapediatrics.2024.5542

Till, C; Green, R; Flora, D; Hornung, R; Martinez-Mier, EA; Blazer, M; Farmus, L; Ayotte, P; Muckle, G; Lanphear, B. (2020). Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environ Int 134: 105315.

U.S. Department of Health and Human Services. (2015). U.S. Public health service recommendation for fluoride concentration in drinking water for the prevention of dental caries. Public Health Rep 130: 318-331.

U.S. EPA (U.S. Environmental Protection Agency). (1986a). Guidelines for carcinogen risk assessment. (EPA/630/R-00/004). Washington, DC. https://assessments.epa.gov/risk/document/&deid%3D54933

U.S. EPA (U.S. Environmental Protection Agency). (1986b). National primary and secondary drinking water regulations; fluoride; final rule. Fed Regist 51: 11395-11412.

U.S. EPA (U.S. Environmental Protection Agency). (1987). Fluorine (soluble fluoride); CASRN 7782-41-4. Integrated Risk Information System (IRIS) chemical assessment summary. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0053_summary.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1996). Reregistration Eligibility Decision (RED) for cryolite. (EPA-738-R-96-016). Washington, DC: U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances. https://www.fluoridealert.org/wp-content/uploads/cryolite.epa_.red_.1996.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2003). Six-year review chemical contaminants health effects technical support document. (EPA 822-R-03-008). Washington, DC: United States Environmental Protection Agency, Office of Water, Office of Science and Technology, Health and Ecological Criteria Division. https://www.epa.gov/sites/default/files/2014-12/documents/822r03008.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2006). Approaches for the application of Physiologically Based Pharmacokinetic (PBPK) models and supporting data in risk assessment (final report) [EPA Report] (pp. 1-123). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668

U.S. EPA (U.S. Environmental Protection Agency). (2007). Reregistration Eligibility Decision (RED) for sodium fluoride (pp. 71). (EPA 739-R-07-010). U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1006M15.txt

U.S. EPA (U.S. Environmental Protection Agency). (2008a). Fluoride: Dose-response analysis for non-cancer effects. Dental fluorosis: Evaluations of key studies [EPA Report]. (EPA 820-R-10-019). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100N4KD.txt

U.S. EPA (U.S. Environmental Protection Agency). (2008b). Fluoride: Dose-response analysis for non-cancer effects. Fluoride-related skeletal effects: Evaluation of key studies [EPA Report]. (EPA 820-R-10-017). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://www.epa.gov/sites/default/files/2019-03/documents/fluoride-related-skeletal-effects.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2010a). Fluoride: Dose-response analysis for non-cancer effects. Washington, DC https://www.epa.gov/sites/default/files/2019-03/documents/fluoride-dose-response-noncancer-effects.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2010b). Fluoride: Exposure and relative source contribution analysis. (820R10015). Washington, DC. https://nepis.epa.gov/Exe/ZyPDF.cgi/P100N49K.PDF?Dockey=P100N49K.PDF

U.S. EPA (U.S. Environmental Protection Agency). (2014). Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation. Washington, DC. https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2016). Six-year review 3 - Health effects assessment for existing chemical and radionuclide national primary drinking water regulations - summary report. (EPA 822-R-16-008). U.S. Environmental Protection Agency, Office of Water. https://www.epa.gov/sites/default/files/2016-12/documents/822r16008.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2017). National primary drinking water regulations; Announcement of the results of EPA's review of existing drinking water standards and request for public comment and/or information on related issues. (pp. 3518-3552). (2016-31262). Washington, DC https://www.federalregister.gov/documents/2017/01/11/2016-31262/national-primary-drinking-water-regulations-announcement-of-the-results-of-epas-review-of-existing

U.S. EPA (U.S. Environmental Protection Agency). (2019). Systematic review protocol for the polychlorinated biphenyls (PCBs) noncancer IRIS assessment (preliminary assessment materials) [EPA Report]. (EPA/635/R-19/201). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment, Integrated Risk Information System. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=237359

U.S. EPA (U.S. Environmental Protection Agency). (2020). Safe drinking water act-(Title XIV of public health service act). 8. https://www.epa.gov/sites/default/files/2020-05/documents/safe_drinking_water_act-title_xiv_of_public_health_service_act.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2022). ORD staff handbook for developing IRIS assessments. (EPA600R22268). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=356370

U.S. EPA (U.S. Environmental Protection Agency). (2024a). Final human health toxicity assessment for perfluorooctane sulfonic acid (PFOS) and related salts. Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2024b). Final human health toxicity assessment for perfluorooctanoic acid (PFOA) and related salts. Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2024c). National primary drinking water regulations; Announcement of the results of EPA's fourth review of existing drinking water standards. Washington, DC

U.S. EPA (U.S. Environmental Protection Agency). (2024d). Results of the health effects assessment for the fourth six-year review of existing chemical and radionuclide national primary drinking water standards. (EPA-815-R-24-020). Washington, DC: U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division. https://www.epa.gov/system/files/documents/2024-04/syr4-health-effects-support-document_508.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2025a, 04/07/2025). EPA will expeditiously review new science on fluoride in drinking water. Available online at https://www.epa.gov/newsreleases/epa-will-expeditiously-review-new-science-fluoride-drinking-water (accessed 01/09/2026).

U.S. EPA (U.S. Environmental Protection Agency). (2025b). Updated problem formulation and protocol for the inorganic arsenic IRIS assessment. Washington, DC Systematic Review Protocol for the Inorganic Arsenic IRIS Assessment

Underwood, EJ. (1977). Trace elements in human and animal nutrition (4 ed.). New York, NY: Academic Press. http://dx.doi.org/10.1016/B978-0-12-709065-8.X5001-9

United States Executive Office of the President Donald Trump. (2025). Executive order 14303—Restoring gold standard science. Available online at https://www.govinfo.gov/app/details/DCPD-202500636 (accessed 01/09/2026).

Valdez Jiménez, L; López Guzmán, OD; Cervantes Flores, M; Costilla-Salazar, R; Calderón Hernández, J; Alcaraz Contreras, Y; Rocha-Amador, DO. (2017). In utero exposure to fluoride and cognitive development delay in infants. NeuroToxicology 59: 65-70.

Varghese, A; Cawley, M; Hong, T. (2018). Supervised clustering for automated document classification and prioritization: A case study using toxicological abstracts. Environ Syst Decis 38: 398-414. http://dx.doi.org/10.1007/s10669-017-9670-5

Vieira, AP; Mousny M Fau - Maia, R; Maia R Fau - Hancock, R; Hancock R Fau - Everett, ET; Everett Et Fau - Grynpas, MD; Grynpas, MD. (2005). Assessment of teeth as biomarkers for skeletal fluoride exposure. Osteoporos Int 16: 1576-1582.

WHO (World Health Organization). (2004). Fluoride in drinking-water. Background document for development of WHO guidelines for drinking-water quality. (WHO/SDE/WSH/03.04/96). Geneva. https://www.who.int/docs/default-source/wash-documents/wash-chemicals/fluoride-background-document.pdf

Yeung, CA. (2014). Some beneficial effect on root caries from use of higher concentration fluoride toothpaste (5000 ppm F). Evid Based Dent 15: 8-9.

# Appendix A. Survey of Published Fluoride Toxicity Assessments and Toxicity Values

Several authoritative sources were searched to identify published reports and toxicity values for oral fluoride exposure. Results from this search are presented in Table 2-1 (noncancer health effect reference values) and Table 2-2 (cancer classifications).

**Table A-1. Sources Used to Identify Published Toxicity Assessments and Toxicity Values (when applicable) for Oral Fluoride Exposure**

| Source | Fluoride Assessments | Noncancer | Cancer |
|---|---|---|---|
| EPA IRIS Chemical Assessment Summaries and Toxicological Reviews | U.S. EPA (1987) | Yes | No |
| EPA OW HA documents and HESDs | U.S. EPA (2010a) | Yes | No |
| EPA PPRTV support documents | N/A | N/A | N/A |
| EPA TSCA Risk Evaluations and other technical support documents | N/A | N/A | N/A |
| EPA OPP HHRAs and RED documents | U.S. EPA (2007), U.S. EPA (1996) | Yes[a] | Yes |
| CDC's ATSDR Toxicological Profiles | ATSDR (2003) | Yes | Yes |
| CalEPA Public Health Goal support documents | OEHHA (2008), OEHHA (2011b) | Yes | Yes |
| EFSA Scientific Output Publications | EFSA Scientific Committee (2025) | Yes | Yes |
| Health Canada Drinking Water Guidelines support documents | Health Canada (2010), Health Canada (2024), Taher et al. (2024) | Yes | Yes |
| WHO Drinking Water Quality Guidelines documents | WHO (2004), IARC (1987b) | Yes[a] | Yes |

EPA = Environmental Protection Agency; IRIS = Integrated Risk Information System; OW = Office of Water; HA = Health Advisory; HESD = Health Effects Support Documents; PPRTV = Provisional Peer-Reviewed Toxicity Value; TSCA = Toxic Substances Control Act; OPP = Office of Pesticide Programs; RED = Reregistration Eligibility Decisions; CDC = Centers for Disease Control and Prevention; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; EFSA = European Food Safety Agency; WHO = World Health Organization.

[a] U.S. EPA (1996), U.S. EPA (2007) and WHO (2004) summarized noncancer health outcomes following fluoride exposure but did not derive oral reference doses.

# Appendix B. Literature Search and Screening Methods

The literature search and screening processes described in this section were used to conduct a SEM and identify an initial literature inventory for fluoride. The resulting literature inventory is presented in Section 4.

## B.1. Literature Search Strategies

### B.1.1. Database Searches

Database searches were conducted in PubMed and Web of Science using the search terms in Table B-1. The searches were conducted with no date limitations and the results were filtered to English language studies. The search terms were written to be inclusive of all English language studies that use the chemical term or its synonyms, and therefore all PECO and exposure results are captured in a single search. The sources used to pull chemical synonyms included the following: CompTox (only "Valid" and "Good" synonyms), ChemIDPlus, Cameo Chemicals, medical subject headings (MeSH) Dictionary (PubMed only), previous EPA/OW searches (SYR4, Contaminant Candidate List 5, Contaminant Candidate List 6), and consultation with subject matter experts. The chemical identifiers used were limited to the Chemical Abstracts Service Registry Number (CASRN), the US EPA CompTox DTXSID Number, and the Unique Ingredient Identifier (UNII) used by the US Food and Drug Administration.

**Table B-1. Database Search Strategies for Fluoride**

| Source | Search Strategy | Number of Records[a,b] |
|---|---|---|
| **Web of Science** | TS=("16984-48-8" OR "DTXSID9049617" OR "florinate" OR "florinated" OR "fluoridate" OR "fluoridated" OR "Fluoride" OR "Fluorides" OR "fluorinate" OR "fluorinated" OR "Fluorine" OR "fluorosis" OR "fluridate" OR "fluridated" OR "FLUORIDE-ION" OR "Hydrofluoric acid, ion(1-)" OR "hydrofluosilicic acid" OR "Perfluoride" OR "Sodium silicofluoride" OR "UNII-Q80VPU408O") | **Total references:** 235,996<br><br>**Limited to English only:** 227,384 |
| **PubMed** | ("16984-48-8"[rn] OR "16984-48-8"[tiab] OR "DTXSID9049617"[tiab] OR "florinate"[tiab] OR "florinated"[tiab] OR "fluoridate"[tiab] OR "fluoridated"[tiab] OR "Fluoride"[tiab] OR "Fluorides"[mh] OR "Fluorides"[tiab] OR "fluorinate"[tiab] OR "fluorinated"[tiab] OR "Fluorine"[tiab] OR "fluorosis"[tiab] OR "Fluorosis, Dental"[mh] OR "fluridate"[tiab] OR "fluridated"[tiab] OR "FLURORIDE-ION"[tiab] OR "Hydrofluoric acid, ion(1-)"[tiab] OR "hydrofluosilicic acid"[tiab] OR "Perfluoride"[tiab] OR "Sodium silicofluoride"[tiab] OR "UNII-Q80VPU408O"[tiab]) | **Total references:** 102,955<br><br>**Limited to English only:** 94,516 |
| **Total** | Unique items discovered using this search strategy. | **Limited to English only:** 268,647 |

[a] Database searches were conducted on November 1, 2024.

[b] "Total references" represents all records identified using the search terms. "Limited to English only" represents that number of references remaining after filtering the results for English language.

### B.1.2. Crosswalk with Published Fluoride Toxicity Assessments and Other Health Effect Reports and Data Sources

In addition to database literature searching, published assessments by EPA and other authoritative sources were reviewed to identify studies cited with hazard information, which were then compared to the database search results. Studies that were not identified in the database search results were added to the review. The following assessments were reviewed to identify additional studies:

- EPA's Fluoride Dose-Response Analysis for Non-Cancer Effects – Dental Fluorosis: Evaluations of Key Studies (U.S. EPA, 2008a)
- EPA's Fluoride Dose-Response Analysis for Non-Cancer Effects – Fluoride-Related Skeletal Effects: Evaluations of Key Studies (U.S. EPA, 2008b)
- EPA's Fluoride Dose-Response Analysis for Non-Cancer Effects (U.S. EPA, 2010b)
- National Research Council's (NRC) Fluoride in Drinking Water: A Scientific Review of EPA's Standards (NRC, 2006)
- NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review (NTP, 2024)
- Health Canada's Guidelines for Canadian Drinking Water Quality: Guideline Technical Document –Fluoride (Health Canada, 2010)
- Taher et al.'s "Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water" (Taher et al., 2024) associated with the 2023 Health Canada Panel Report (Health Canada, 2024)
- EFSA Scientific Committee's Updated consumer risk assessment of fluoride in food and drinking water including the contribution from other sources of oral exposure (EFSA Scientific Committee, 2025)

Additionally, literature prioritization files from EPA's SYR4 (U.S. EPA, 2024d) process for fluoride and studies referenced in the American Dental Association (ADA) Letter to the EPA Administrator (American Dental Association, 2025) were reviewed to identify potentially relevant studies. These published assessments contained a total of 320 studies of fluoride that were not identified in the database searches or were excluded during prioritization processes and were advanced to title-abstract screening.

## B.2. Literature Screening Strategies

Prior to literature screening, records were deduplicated to remove records that were identified from multiple sources.

### B.2.1. Initial Problem Formulation PECO Criteria

Literature prioritization and title-abstract screening were guided by the initial problem formulation PECO for fluoride (Table B-2), which was broad and included all outcomes in both humans and experimental animal models. Studies that met the problem formulation PECO criteria were included during title-abstract screening.

**Table B-2. Initial Problem Formulation Populations, Exposures, Comparators, and Outcomes Criteria for the Fluoride Assessment[a]**

| PECO Element | Evidence[b] |
|---|---|
| Populations | Human: Any population and lifestage (occupational or general population, including children and other sensitive populations).<br>Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, *in utero*, lactation, peripubertal, and adult stages). |
| Exposures | Relevant forms: Any exposure to fluoride, and/or related forms, including but not limited to: Fluoride (CASRN 16984-48-8).<br>Other names/forms:<br>• ammonium fluoride<br>• calcium fluoride<br>• disodium hexafluorosilicate<br>• fluoride ion<br>• fluorine<br>• fluorosilic acid<br>• hydrofluoric acid, ion(1-)<br>• hydrofluorosilicate<br>• hydrofluosilicic acid<br>• perfluoride<br>• potassium fluoride<br>• sodium hexafluorosilicate<br>• sodium fluoride<br>• sodium fluorosilicate<br>• sodium silicofluoride<br>• amine fluoride<br>• Olafur<br>The following forms should also be included if mentioned in the context of exposure via toothpaste: sodium monofluorophosphate, stannous fluoride, amine fluoride, and acidulated phosphate fluoride.<br>Aluminum fluoride will be excluded due to complex interactions with fluoride.<br>All PFAS chemicals and fluoridated organic compounds (e.g., fluoridated pyrimidines) will be excluded.<br>Human: Any exposure to the chemicals listed above via oral routes or unknown/multiple routes (e.g., biomonitoring studies). Other exposure routes, including inhalation or dermal, will be excluded and tagged as supplemental.<br>Animal: Any exposure to the chemicals listed above via oral routes. Other exposure routes, including inhalation, dermal, injection, or unknown/multiple routes will be excluded and tagged as supplemental. Studies involving exposures to mixtures will be included only if they include exposure to the chemical of interest alone. Studies with fewer than 28 days of dosing, with the exception of reproductive, developmental, immune, and neurological health outcome studies, will be excluded and tagged as supplemental. Animal studies with only one dose group (e.g., control and one dose group only) will be excluded and tagged as supplemental. |
| Comparators | Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of the chemical or interest, or exposure to the chemical of interest for shorter periods of time. Case reports and case series will be excluded and tagged as supplemental if other PECO parameters are met.<br>Animal: A concurrent control group exposed to vehicle-only treatment or untreated control. Controls with low levels of fluoride in drinking water (tap water) and animal feed should be included if other PECO parameters are met. |
| Outcomes | All health outcomes (both cancer and noncancer). |
| PBPK Models | Studies describing PK or PBPK models will be included. |

| PECO Element | Evidence[b] |
|---|---|
| | Classical PK or Dosimetry Model Studies: Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, where movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to ADME data. This category is for papers that provide detailed descriptions of PK models, that are not a PBPK model.<br>Note: ADME studies often report classical PK parameters, such as bioavailability (fraction of an oral dose absorbed), volume of distribution, clearance rate, or half-live(s). If a paper only provides such results in tables with minimal description of the underlying model or software (i.e., uses standard PK software without elaboration), including "noncompartmental analysis," it should be listed only as a supplemental material ADME study.<br>PBPK or Mechanistic Dosimetry Model Studies: PBPK models represent the body as various compartments (e.g., liver, lung, slowly perfused tissue, richly perfused tissue) to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism and elimination, and thereby estimate concentrations in blood or target tissues. |

PECO = populations, exposures, comparators, and outcomes; CASRN = Chemical Abstracts Service registry number; PFAS = per- and polyfluoroalkyl substances; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetic; ADME = absorption, distribution, metabolism, and excretion.

[a] The initial problem formulation PECO criteria for the Fluoride Assessment was used to identify studies for inclusion during title-abstract and full-text screening.

[b] In addition to studies meeting the problem formulation PECO criteria, mechanistic studies (including *in vitro* studies) were tracked as included during title-abstract screening to ensure that they were prioritized by the machine learning model in SWIFT-Active Screener software (see Section B.2.3). Mechanistic studies were tracked as supplemental during full-text screening.

## B.2.2. Literature Prioritization using Artificial Intelligence and Other Automated Processes

Natural language processing and machine learning techniques were used to identify the most relevant records for title-abstract screening. Figure B-1 provides an overview of the steps taken to prioritize the literature identified.

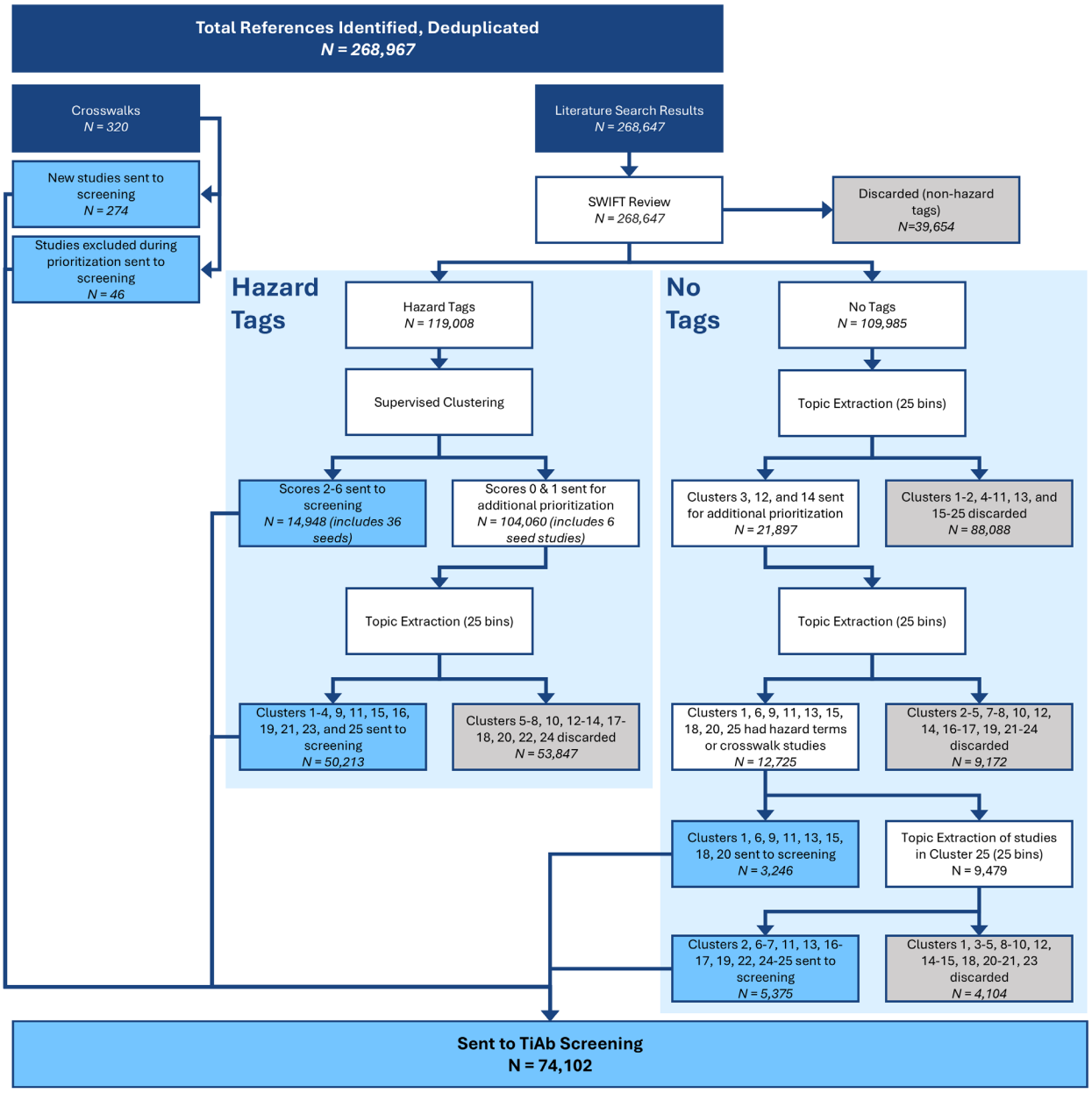


**Figure B-1. Overview of Literature Prioritization Workflow**

Dark blue boxes capture efforts to identify literature. Light blue boxes capture records that advanced to title-abstract screening. Gray boxes capture records that were excluded from the workflow based on prioritization outcomes. After identification, studies underwent SWIFT-Review filtering to identify studies with hazard information (see below for a detailed description of SWIFT-Review; evidence stream filters available online at https://www.sciome.com/swift-review/searchstrategies/). Following SWIFT-Review, studies underwent additional prioritization using either supervised clustering or topic extraction methods to obtain the final group of studies for title-abstract screening. "Score" refers to outputs from supervised clustering prioritization (see below for a detailed description of supervised clustering). "Cluster" refers to outputs from topic extraction prioritization (see below for a detailed description of topic extraction).

### B.2.2.1. SWIFT-Review

All unique records identified in the database searches were imported into SWIFT-Review software (https://www.sciome.com/swift-review/) to identify those most likely to be applicable to the

scope of EPA's toxicity assessment. Briefly, SWIFT-Review has preset literature search strategies ("filters") developed and applied by information specialists to identify studies more likely to be useful for identifying human health content. The filters function like a typical search strategy in which studies are tagged as belonging to a certain filter if the terms in the filter literature search strategy appear in title, abstract, keyword or MeSH fields. The details of the search strategies that underlie the filters are available online (https://www.sciome.com/swift-review/searchstrategies/). The following SWIFT-Review evidence stream filters were applied (referred to as "hazard" tags in the following sections):

- Animal (human health models)
- Animal (all)
- Human
- Epidemiologic quantitative analyses
- In vitro

In addition, studies that SWIFT-Review was unable to categorize to an evidence stream ("no tag") were retained for further review. After SWIFT-Review filtering (n = 119,008 studies identified using the evidence stream filters), additional prioritization tools (i.e., topic extraction and supervised clustering) were then implemented as described below.

Of note, there were 46 records identified from the database searches that were excluded during literature prioritization but were also identified as being cited in published assessments of fluoride (see Section B.1). Because of their potential relevance, these 46 studies were forwarded to title-abstract screening.

### B.2.2.2. Prioritization of PECO Studies

For studies that received hazard tags following application of the SWIFT-Review evidence stream filters (listed above), additional prioritization to identify studies most relevant to dose-response was conducted using supervised clustering in ICF's Litstream® software. Clustering has been used in previous EPA assessments (U.S. EPA, 2025b, 2019) to cull large literature databases and efficiently identify studies most likely to meet the PECO criteria. Supervised clustering combines aspects of unsupervised machine learning and supervised machine learning to classify documents based on a small training set of relevant literature (or "seed studies") (Varghese et al., 2018). Ensemble supervised clustering in Litstream uses six clustering algorithms. If any one of the six models finds a document to be relevant, it is tagged as such (thus erring on the side of inclusion/retention). An ensemble score is generated by adding the result of the six models. A document with an ensemble score of six indicates the document was found to be relevant by all six models. Studies were prioritized for screening by descending order of ensemble score (6 to 0).

Forty-two PECO-relevant studies (listed in Section B.2.2.2.1) were selected from previous EPA assessments of fluoride and the list of studies that received hazard tags during SWIFT-Review filtering to serve as seeds for the supervised clustering of fluoride literature. The seed studies represent a range of PECO relevant topics (e.g., epidemiology studies, animal toxicology studies, and studies that included mechanistic findings) and exposure routes (e.g., drinking water and oral exposures in addition to topical application to the oral cavity). Supervised clustering results are provided below in Table B-3.

**Table B-3. Supervised Clustering Results for Fluoride Literature Following SWIFT-Review Filtering**

| Ensemble Score | Counts | Seeds in Cluster |
|---|---|---|
| 0 | 89,109 | 2 |
| 1 | 14,951 | 4 |
| 2 | 6,192 | 7 |
| 3 | 1,876 | 5 |
| 4 | 1,968 | 2 |
| 5 | 4,198 | 15 |
| 6 | 714 | 7 |
| **Grand Total** | 119,008 | 42 |

### B.2.2.2.1. Seed Studies for Supervised Clustering of Fluoride Literature following SWIFT-Review Filtering

- Components of drinking water and risk of cognitive impairment in the elderly (Jacqmin et al., 1994)
- Aluminium and fluoride in drinking water in relation to later dementia risk (Russ et al., 2020)
- Alterations in the memory of rat offspring exposed to low levels of fluoride during gestation and lactation: Involvement of the α7 nicotinic receptor and oxidative stress (Bartos et al., 2018)
- Fluoride exposure from infant formula and child IQ in a Canadian birth cohort (Till et al., 2020)
- Decreased intelligence in children and exposure to fluoride and arsenic in drinking water (Rocha-Amador et al., 2007)
- Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth (Riddell et al., 2019)
- Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 Years of Age in Mexico (Bashash et al., 2017)
- Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada (Green et al., 2019)
- Down syndrome, water fluoridation, and maternal age (Erickson, 1980)
- Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study (Khandare et al., 2018)
- Fluoride exposure and indicators of thyroid functioning in the Canadian population: implications for community water fluoridation (Barberio et al., 2017a)
- In utero exposure to fluoride and cognitive development delay in infants (Valdez Jiménez et al., 2017)
- Fluoride exposure and reported learning disability diagnosis among Canadian children: Implications for community water fluoridation (Barberio et al., 2017b)
- Water fluoridation and congenital malformations: no association (Erickson et al., 1976)

- Association Between Osteoarthritis and Water Fluoride Among Tongyu Residents, China, 2019: a Case-Control of Population-Based Study (Sowanou et al., 2022)
- Developmental toxicity evaluation of sodium fluoride administered to rats and rabbits in drinking water (Heindel et al., 1996)
- Changes in Liver Antioxidant Status of Offspring Mice Induced by Maternal Fluoride Exposure During Gestation and Lactation (Niu et al., 2016)
- Association of fluoride exposure with disease burden and neurodevelopment outcomes in children in South Korea (Lee et al., 2024)
- Neurofunctional effects of developmental sodium fluoride exposure in rats (Bera et al., 2007)
- The effect of chronic treatment with fluoride on salivary activity, tooth, and bone in spontaneously hypertensive rats (SHR) (Picco et al., 2014)
- Sodium fluoride causes oxidative stress and apoptosis in the mouse liver (Lu et al., 2017)
- Two-year carcinogenicity study of sodium fluoride in rats (Maurer et al., 1990)
- Effects of Fluoride on SOD and CAT in Testis and Epididymis of Mice (Sun et al., 2018)
- Effects of Perinatal Fluoride Exposure on Short- and Long-Term Memory, Brain Antioxidant Status, and Glutamate Metabolism of Young Rat Pups (Bartos et al., 2019)
- Suppression of male reproduction in rats after exposure to sodium fluoride during early stages of development (Reddy et al., 2007)
- Fluoride exposure and pubertal development in children living in Mexico City (Liu et al., 2019)
- Musculoskeletal problems and fluoride exposure: A cross-sectional study among metal smelting workers (Saha et al., 2016)
- Associations of gestational and early-life exposure to toxic metals and fluoride with a diagnosis of food allergy or atopic eczema at 1 year of age (Kampouri et al., 2023)
- Toxic effects of chronic fluoride ingestion on the upper gastrointestinal tract (Das et al., 1994)
- Dental fluorosis prevalence, severity and associated risk factors in pre-school aged children residing in fluoride deficient regions of Georgia (Sharashenidze et al., 2020)
- Effect of long-term exposure to fluoride in drinking water on risks of bone fractures (Li et al., 2001b)
- Dental caries, its surface susceptibility and dental fluorosis in South India (Acharya, 2005)
- Fluoride exposure and dental fluorosis in Newburgh and Kingston, New York: policy implications (Kumar and Swango, 1999)
- Risk factors for enamel fluorosis in a nonfluoridated population. (Pendrys et al., 1996)
- Risk factors for dental fluorosis in pediatric dental patients (Skotowski et al., 1995)
- Fluorosis risk from early exposure to fluoride toothpaste (Mascarenhas and Burt, 1998)
- Comparative effect of fluoride, essential oil and chlorhexidine mouth rinses on dental plaque and gingivitis in patients with and without dental caries: a randomized controlled trial (Charugundla et al., 2015)
- Some beneficial effect on root caries from use of higher concentration fluoride toothpaste (5000 ppm F) (Yeung, 2014)

- Effects of fluoride on anxiety and depression in mice (Kivrak and Kars, 2012)
- Pathological changes and effect on the learning and memory ability in rats exposed to fluoride and aluminum (Li et al., 2015)
- Impact of 12-week ingestion of sodium fluoride on aggression, sexual behavior, and fertility in adult male rats (Bataineh and Nusier, 2006)
- Effect of fluoride in drinking water on dental caries and IQ in children (Soto-Barreras et al., 2019)

After reviewing the results, the 14,948 studies with ensemble scores 2–6 were forwarded for title-abstract screening, as these scores included seed studies and were predicted to be relevant by at least two models. Ensemble scores 0 and 1 (those generally assumed to be least relevant) also contained seed studies and were further prioritized using topic extraction in Litstream, which clusters references into groups based on similarity of keywords used in the titles and abstracts. Topic extraction identified 25 groups of common terms across the studies in ensemble scores 0 and 1 (Table B-4). EPA identified topic clusters 2, 3, 9, 11, 15, 16, 19, 21, 23 and 25 as groups containing potentially relevant studies based on the topic extraction terms. Importantly, the 6 seed studies contained in supervised clustering ensemble scores 0 and 1 were captured in topic clusters 2 and 21. EPA also identified topic clusters 1 and 4 as containing potentially relevant mechanistic terms. Therefore, EPA advanced the 50,213 studies identified in bins 1, 2, 3, 4, 9, 11, 15, 16, 19, 21, 23 and 25 to title and abstract screening. In total, 65,161 studies that received hazard tags in SWIFT-Review were prioritized for title-abstract screening.

**Table B-4. Topic Extraction of Fluoride Supervised Clustering Ensemble Scores 0 and 1 using 25 Bins**

| Topic Cluster Number | Number of References | Topic Key Words |
|---|---|---|
| *1* | *6,408* | *['activity', 'enzyme', 'protein', 'inhibited', 'protease', 'purified', 'cells', 'inhibitor', 'ph', 'serine', 'inhibitors', 'inhibition', 'proteins', 'acid', 'mm', 'dependent', 'phosphatase', 'binding', 'presence', 'rat']* |
| **2** | **6,512** | **['children', 'dental', 'caries', 'health', 'oral', 'oral health', 'dental caries', 'year', 'prevalence', 'years', 'fluorosis', 'preventive', 'care', 'teeth', 'risk', 'school', 'study', 'age', 'dental fluorosis', 'prevention']** |
| **3** | **1,185** | **['contrast', 'contrast enhanced', 'ultrasound', 'ceus', 'enhanced', 'enhanced ultrasound', 'contrast enhanced ultrasound', 'patients', 'sonovue', 'liver', 'contrast agent', 'enhancement', 'ultrasonography', 'lesions', 'imaging', 'perfusion', 'diagnosis', 'sonography', 'ultrasound ceus', 'agent']** |
| *4* | *1,785* | [*'cyclase', 'adenylate', 'adenylate cyclase', 'cyclase activity', 'adenylate cyclase activity', 'activity', 'stimulated', 'adenyl', 'adenyl cyclase', 'rat', 'stimulation', 'membranes', 'basal', 'enzyme', 'activation', 'hormone', 'isoproterenol', 'adrenergic', 'receptor', 'gtp']* |
| 5 | 1,295 | ['glass ionomer', 'ionomer', 'glass', 'cement', 'resin', 'ionomer cement', 'glass ionomer cement', 'cements', 'release', 'materials', 'gic', 'restorative', 'ionomer cements', 'glass ionomer cements', 'resin modified', 'modified glass', 'resin modified glass', 'restorative materials', 'fuji', 'modified'] |
| 6 | 3,714 | ['18', 'pet', 'imaging', 'positron', 'tomography', 'positron emission', 'emission tomography', 'positron emission tomography', 'fluorine 18', 'emission', 'labeled', '18f', 'brain', 'uptake', 'vivo', 'fluorine', 'pet imaging', '18 labeled', 'radiochemical', 'emission tomography pet'] |
| 7 | 1,188 | ['fuel', 'membranes', 'proton', 'membrane', 'fuel cell', 'fuel cells', 'exchange', 'nafion', 'conductivity', 'proton exchange', 'proton conductivity', 'cell', 'sulfonated', 'exchange membrane', 'polymer', 'poly', 'membrane fuel', 'proton exchange membrane', 'cm', 'exchange membranes'] |
| 8 | 10,042 | ['structure', 'stable', 'crystal', 'temperature', 'calculations', 'fluorine', 'complexes', 'phase', 'energy', 'hydrogen', 'structures', 'atoms', 'state', 'degrees', 'formation', 'properties', 'ray', 'reaction', 'molecular', 'using'] |
| **9** | **2,353** | **['enamel', 'dental enamel', 'human', 'dental', 'human enamel', 'teeth', 'surface', 'vitro', 'tooth', 'uptake', 'caries', 'effect', 'fluorosis', 'remineralization', 'acid', 'enamel surface', 'calcium', 'demineralization', 'tooth enamel', 'surface enamel']** |
| 10 | 8,737 | ['surface', 'films', 'properties', 'film', 'oxide', 'water', 'fluorine', 'coating', 'using', 'high', 'fluorinated', 'doped', 'spectroscopy', 'degrees', 'ray', 'electron', 'coatings', 'prepared', 'based', 'layer'] |
| **11** | **1,183** | **['caries', 'dental caries', 'dental', 'prevention', 'prevention dental', 'prevention dental caries', 'caries prevention', 'children', 'fluorine', 'prophylaxis', 'dental caries prevention', 'dental caries children', 'caries children', 'fluorides', 'water', 'prevention caries', 'caries fluorine', 'fluoridation', 'prophylaxis dental', 'dental caries fluorine']** |
| 12 | 2,737 | ['pvdf', 'piezoelectric', 'vinylidene', 'poly', 'poly vinylidene', 'flexible', 'sensor', 'energy', 'polyvinylidene', 'based', 'output', 'polymer', 'trfe', 'sensors', 'mechanical', 'wearable', 'film', 'high', 'ferroelectric', 'vdf'] |
| 13 | 3,351 | ['nm', 'emission', 'luminescence', 'doped', 'red', 'fluorescence', 'green', 'upconversion', 'ions', 'light', 'excitation', 'er3', 'emitting', 'color', 'detection', 'blue', 'laser', 'fluorescent', 'optical', 'based'] |
| 14 | 2,353 | ['solar', 'solar cells', 'cells', 'perovskite', 'efficiency', 'pscs', 'pce', 'perovskite solar', 'power conversion', 'perovskite solar cells', 'conversion', 'conversion efficiency', 'photovoltaic', 'power conversion efficiency', 'device', 'power', 'layer', 'polymer', 'performance', 'based'] |

| Topic Cluster Number | Number of References | Topic Key Words |
|---|---|---|
| **15** | **20,857** | **['effect', 'sodium', 'bone', 'fluorine', 'human', 'effects', 'study', 'treatment', 'patients', 'cells', 'clinical', 'use', 'using', 'vitro', 'used', 'acid', 'results', 'caries', 'studies', 'rat']** |
| **16** | **718** | **['retinal', 'eyes', 'detachment', 'macular', 'vitrectomy', 'retinal detachment', 'gas', 'surgery', 'visual', 'macular hole', 'tamponade', 'acuity', 'visual acuity', 'hole', 'patients', 'postoperative', 'sf6', 'pars plana', 'plana', 'pars']** |
| 17 | 1,601 | ['sensitized', 'sensitized solar', 'dye', 'dye sensitized', 'dye sensitized solar', 'solar', 'sensitized solar cells', 'solar cells', 'tio2', 'dsscs', 'fto', 'cells', 'efficiency', 'oxide', 'counter', 'tin', 'tin oxide', 'doped', 'fluorine doped', 'doped tin'] |
| 18 | 9,369 | ['compounds', 'synthesis', 'fluorinated', 'derivatives', 'activity', 'reaction', 'fluorine', 'nmr', 'synthesized', 'new', 'substituted', 'compound', 'alpha', 'fluoro', 'acid', 'novel', 'group', 'binding', 'analogues', 'series'] |
| **19** | **1,292** | **['pet', 'ct', 'pet ct', 'bone', '18', 'naf', 'naf pet', 'patients', 'prostate', '18 naf', 'cancer', 'imaging', '18f', 'naf pet ct', 'prostate cancer', 'metastases', 'uptake', 'tomography', '18 naf pet', 'bone metastases']** |
| 20 | 1,865 | ['membrane', 'membranes', 'pvdf', 'flux', 'water', 'separation', 'fouling', 'polyvinylidene', 'pvdf membrane', 'surface', 'distillation', 'membrane distillation', 'pore', 'performance', 'rejection', 'polyvinylidene pvdf', 'poly', 'contact', 'pvdf membranes', 'oil'] |
| **21** | **6,015** | **['enamel', 'group', 'groups', 'control', 'study', 'dentifrice', 'significant', '05', 'treatment', 'dentin', 'test', 'effect', 'containing', 'significantly', 'teeth', 'remineralization', 'plaque', 'lesions', 'specimens', 'caries']** |
| 22 | 3,867 | ['fdg', 'pet', 'fdg pet', 'ct', 'tomography', '18', 'pet ct', 'patients', 'positron emission', 'positron', 'emission tomography', 'positron emission tomography', 'fluorine 18', 'fdg pet ct', '18 fdg', 'fluorodeoxyglucose', 'emission', '18 fluorodeoxyglucose', 'uptake', 'imaging'] |
| **23** | **867** | **['fluorides', 'topical', 'topical application', 'caries', 'application', 'topical fluorides', 'prevention', 'use fluorides', 'effect', 'use', 'caries prevention', 'dental', 'fluorides caries', 'prevention fluorides', 'effect fluorides', 'effect topical', 'topical applications', 'caries prevention fluorides', 'fluorides dental', 'application fluorides']** |
| 24 | 3,728 | ['lithium', 'batteries', 'electrolyte', 'li', 'ion', 'capacity', 'high', 'electrolytes', 'lithium ion', 'ion batteries', 'electrochemical', 'cathode', 'battery', 'performance', 'metal', 'cycling', 'anode', 'solid', 'cycles', 'stability'] |
| **25** | **1,038** | **['osteoporosis', 'bone', 'treatment osteoporosis', 'treatment', 'therapy', 'postmenopausal', 'fractures', 'calcium', 'fracture', 'sodium', 'therapy osteoporosis', 'vitamin', 'patients', 'women', 'postmenopausal osteoporosis', 'vertebral', 'bone mineral', 'bone mass', 'bone loss', 'mineral']** |

**Bold font** indicates topic clusters that appear to include studies meeting populations, exposures, comparators, and outcomes (PECO) criteria based on the listed terms. N = 42,020 studies. *Italicized font* indicates topic clusters that appear to include mechanistic information based on the listed terms. N = 8,193 studies.

### B.2.2.3. Prioritization of "No Tag" Studies

Studies that did not receive a tag during SWIFT-Review filtering ("no tag" above) underwent further review to identify the likelihood that they met the PECO criteria. Topic extraction was conducted using ICF's Litstream tool as described above (Section B.2.2.2). This was carried out in three phases:

1) All "no tag" references were placed into 25 groups ("topics") according to the keywords commonly used in the titles and abstracts (Table B-5). These 25 topics were reviewed to identify relevant terminology. Topic Cluster 12 included terms such as "caries," "fluorosis," and "teeth" that were presumed to refer to studies with relevant information. Additionally, Clusters 3, 12, and 14 also included studies identified in the crosswalk with published assessments, suggesting that these clusters included some relevant literature. These three clusters were further refined as described below. The other topic clusters in Table B-5 did not include relevant terminology and were excluded from further consideration.
2) To further refine the literature to forward to title-abstract screening, an additional targeted extraction was conducted of the 21,897 studies from clusters 3, 12, and 14 (Table B-6). Clusters 1, 6, 9, 11, 13, 15, 18, 20, and 25 (n = 12,725 studies) from this additional targeted extraction appeared to include relevant information based on the listed terms. The subset of studies from Clusters 1, 6, 9, 11, 13, 15, 18, and 20 that did not overlap with studies identified in the crosswalks (n = 3,246) were forwarded to SWIFT-Active Screener for title-abstract screening.
3) After the topic extraction in Table B-6, many studies (n = 9,479) were included in Cluster 25, which appeared to have relevant terms. An additional topic extraction was conducted on Cluster 25 to identify potentially relevant studies (Table B-7). Studies in Clusters 2, 6, 7, 11, 13, 16, 17, 19, 22, 24, and 25 that did not overlap with studies identified in the crosswalks (n = 5,375) were forwarded to SWIFT-Active Screener for title-abstract screening.

In total, 8,621 studies with no tag following SWIFT-Review were forwarded for title-abstract screening.

**Table B-5. Topic Extraction Results for Fluoride Literature with No Tag in SWIFT-Review**

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| 1 | 4,036 | 'catalyzed', 'reaction', 'coupling', 'aryl', 'palladium', 'cross coupling', 'synthesis', 'mild', 'alkenes', 'radical', 'cross', 'functional', 'palladium catalyzed', 'conditions', 'copper', 'yields', 'bond', 'reactions', 'group', 'developed' |
| 2 | 5,773 | 'complexes', 'crystal', 'structure', 'ii', 'ray', 'complex', 'ligands', 'ligand', 'structures', 'crystal structure', 'iii', 'angstrom', 'metal', 'single', 'compounds', 'single crystal', 'diffraction', 'group', 'nmr', 'coordination' |
| **3** | **15,179** | **'sodium', 'effect', 'calcium', 'water', 'ion', 'acid', 'lithium', 'study', 'solutions', 'effects', 'reactions', 'new', 'reaction', 'synthesis', 'ions', 'activity', 'chloride', 'potassium', 'formation', 'fluorine'** |
| 4 | 4,187 | 'pvdf', 'piezoelectric', 'polyvinylidene', 'composites', 'composite', 'polymer', 'properties', 'poly', 'poly vinylidene', 'polyvinylidene pvdf', 'vinylidene', 'films', 'dielectric', 'phase', 'mechanical', 'film', 'electrical', 'based', 'nanocomposites', 'high' |
| 5 | 2,265 | 'poly', 'vinylidene', 'poly vinylidene', 'pvdf', 'blends', 'polymer', 'crystallization', 'phase', 'methacrylate', 'poly methyl', 'methyl methacrylate', 'electrolyte', 'poly methyl methacrylate', 'hfp', 'ionic', 'conductivity', 'blend', 'electrolytes', 'temperature', 'pmma' |
| 6 | 5,386 | 'fluorinated', 'synthesis', 'synthesis fluorinated', 'compounds', 'new', 'properties', 'derivatives', 'polymers', 'new fluorinated', 'highly fluorinated', 'novel', 'partially fluorinated', 'partially', 'reactions', 'highly', 'fluorinated compounds', 'novel fluorinated', 'analogs', 'liquid', 'acids' |
| 7 | 1,445 | 'ferroelectric', 'trifluoroethylene', 'trfe', 'vinylidene trifluoroethylene', 'vdf', 'vdf trfe', 'vinylidene', 'copolymer', 'poly vinylidene trifluoroethylene', 'polarization', 'films', 'poly', 'poly vinylidene', 'copolymers', 'field', 'polymer', 'trifluoroethylene vdf', 'trifluoroethylene vdf trfe', 'dielectric', 'switching' |
| 8 | 547 | 'dot center', 'dot center dot', 'center dot center', 'center dot', 'dot', 'center', 'hydrogen', 'interactions', 'center dot hydrogen', 'dot hydrogen', 'hydrogen bonds', 'bonds', 'crystal', 'pi', 'dot hydrogen bonds', 'bond', 'center dot pi', 'dot pi', 'intermolecular', 'complexes' |
| 9 | 6,813 | 'films', 'surface', 'film', 'plasma', 'oxide', 'fluorine', 'deposition', 'etching', 'spectroscopy', 'layer', 'ray', 'deposited', 'doped', 'tin', 'silicon', 'using', 'electron', 'si', 'fluorine doped', 'tin oxide' |
| 10 | 1,987 | 'glasses', 'glass', 'doped', 'ions', 'optical', 'er3', 'emission', 'glass ceramics', 'properties', 'absorption', 'ceramics', 'spectra', 'heavy metal', 'transition', 'luminescence', 'zrf4', 'baf2', 'crystallization', 'heavy', 'fluorescence' |
| 11 | 1,697 | '18', '18f', 'fluorine 18', 'pet', 'imaging', 'tomography', 'positron', 'positron emission', 'emission tomography', 'positron emission tomography', 'fluorine', 'labeled', 'emission', '18 labeled', 'radiochemical', 'fdg', 'labeling', 'pet ct', 'ct', 'synthesis' |
| **12** | **1,480** | **['caries', 'dental', 'enamel', 'fluorosis', 'dental caries', 'dental fluorosis', 'prevention', 'effect', 'uptake', 'topical', 'caries prevention', 'fluoridated', 'dental enamel', 'lesions', 'plaque', 'remineralization', 'prevention dental', 'prophylaxis', 'prevention dental caries', 'teeth']** |
| 13 | 9,277 | 'synthesis', 'reaction', 'alpha', 'beta', 'yields', 'derivatives', 'trifluoromethyl', 'substituted', 'compounds', 'reactions', 'acid', 'corresponding', 'fluorinated', 'fluoro', 'amino', 'products', 'ketones', 'group', 'conditions', 'good' |
| **14** | **5,238** | **'fluorine', 'fluorine containing', 'containing', 'compounds', 'fluorine compounds', 'fluorine chemistry', 'chemistry', 'synthesis', 'reactions', 'synthesis fluorine', 'organic', 'atoms', 'reaction', 'fluorine atoms', 'synthesis fluorine containing', 'organic fluorine', 'chlorine', 'properties', 'aromatic', 'substituted'** |
| 15 | 456 | 'ionomer', 'glass ionomer', 'release', 'glass', 'cements', 'ionomer cements', 'glass ionomer cements', 'cement', 'release glass', 'restorative', 'ionomer cement', 'glass ionomer cement', 'release glass ionomer', 'resin', 'glass ionomers', 'ionomers', 'restorative materials', 'materials', 'resin modified', 'modified glass' |

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| 16 | 2,362 | 'membrane', 'membranes', 'pvdf', 'water', 'flux', 'separation', 'surface', 'fouling', 'polyvinylidene', 'performance', 'pvdf membrane', 'poly', 'pore', 'pvdf membranes', 'prepared', 'properties', 'polyvinylidene pvdf', 'contact', 'hollow', 'poly vinylidene' |
| 17 | 2,763 | 'fluorides', 'earth', 'metal fluorides', 'earth fluorides', 'alkaline earth', 'alkaline', 'alkaline earth fluorides', 'metal', 'alkali', 'synthesis', 'rare', 'rare earth', 'transition metal fluorides', 'reactions', 'new', 'structure', 'acid fluorides', 'transition', 'transition metal', 'uranium' |
| 18 | 5,133 | 'laser', 'doped', 'crystals', 'optical', 'nm', 'luminescence', 'emission', 'fiber', 'ions', 'excitation', 'absorption', 'single', 'wavelength', 'crystal', 'energy', 'power', 'spectra', 'earth', 'radiation', 'high' |
| 19 | 1,845 | 'hydrogen', 'anhydrous hydrogen', 'anhydrous', 'hydrogen bonding', 'bonding', 'fluorine', 'hydrogen bond', 'liquid hydrogen', 'fluorine hydrogen', 'bond', 'reaction', 'liquid', 'hydrogen fluorine', 'hydrogen bonds', 'hf', 'reactions', 'bonds', 'water', 'acid', 'complexes' |
| 20 | 2,267 | 'nmr', '19', 'resonance', 'magnetic resonance', 'magnetic', 'nuclear', 'nuclear magnetic', 'nuclear magnetic resonance', 'fluorine', '19 nmr', 'spin', '19f', 'spectra', 'spectroscopy', 'nmr spectra', 'chemical', 'fluorine 19', 'shifts', '19 nuclear', 'nmr spectroscopy' |
| 21 | 716 | 'spectrum', 'rotational', 'nu', 'vibrational', 'microwave', 'constants', 'spectra', 'microwave spectrum', 'rotation', 'state', 'band', 'cm', 'states', 'ground', 'infrared', 'resolution', 'transitions', 'nu nu', 'rotational spectrum', 'structure' |
| 22 | 1,904 | 'anion', 'anions', 'fluorescence', 'fluorescent', 'binding', 'receptor', 'detection', 'sensing', 'based', 'colorimetric', 'recognition', 'selective', 'receptors', 'sensor', 'ions', 'chemosensor', 'synthesized', 'ion', 'nmr', 'selectivity' |
| 23 | 20,438 | 'surface', 'high', 'temperature', 'properties', 'using', 'based', 'results', 'materials', 'fluorinated', 'degrees', 'fluorine', 'phase', 'used', 'low', 'performance', 'different', 'adsorption', 'study', 'effect', 'process' |
| 24 | 1,694 | 'determination', 'determination fluorine', 'electrode', 'selective electrode', 'ion', 'selective', 'ion selective', 'fluorine', 'method', 'ion selective electrode', 'potentiometric', 'spectrophotometric', 'method determination', 'using', 'spectrophotometric determination', 'samples', 'detection', 'chromatography', 'analysis', 'spectrometry' |
| 25 | 5,097 | 'calculations', 'energy', 'initio', 'ab initio', 'ab', 'energies', 'experimental', 'molecular', 'calculated', 'fluorine', 'bond', 'state', 'results', 'vibrational', 'electronic', 'atoms', 'molecules', 'theoretical', 'theory', 'states' |

**Bold font** indicates topic clusters that appear to include studies that meet the populations, exposures, comparators, and outcomes (PECO) criteria based on the listed terms or included studies identified in the crosswalk with published assessments. N = 21,897 studies.

**Table B-6. Targeted Topic Extraction Results for Fluoride Literature with No Tag in SWIFT-Review in Clusters 3, 12, and 14**

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| **1** | **557** | **'water', 'fluorosis', 'drinking', 'drinking water', 'fluoridation', 'water fluoridation', 'levels', 'skeletal fluorosis', 'skeletal', 'endemic', 'content', 'endemic fluorosis', 'content drinking', 'content drinking water', 'removal', 'water supply', 'levels drinking', 'supply', 'levels drinking water', 'problem'** |
| 2 | 603 | 'ions', 'acid', 'solutions', 'fluorine ions', 'acid solutions', 'aqueous', 'effect', 'phosphoric', 'presence', 'phosphoric acid', 'fluorine', 'extraction', 'nitric', 'solution', 'nitric acid', 'presence ions', 'hydrofluoric acid', 'hydrofluoric', 'sulfuric', 'production' |
| 3 | 356 | 'catalytic', 'modified', 'catalysts', 'activity', 'catalytic activity', 'catalyst', 'fluorine', 'reactions', 'reaction', 'using', 'active', 'catalytic properties', 'properties', 'site', 'acid', 'effect', 'lewis', 'supported', 'alumina', 'presence' |
| 4 | 446 | 'fluoro', 'phosphorus', 'fluorine', 'synthesis', 'compounds', 'properties', 'phosphorus fluorine', 'chemistry', 'containing', 'new', 'fluorine phosphorus', 'atom', 'reaction', 'reactions', 'derivatives', 'substituted', 'activity', 'chemical', 'substituents', 'deoxy' |
| 5 | 2,114 | 'fluorine', 'carbon', 'chlorine', 'atomic', 'atomic fluorine', 'fluorine substituted', 'substituted', 'reaction', 'carbon fluorine', 'atom', 'silicon', 'fluorine atom', 'reactions', 'study', 'synthesis', 'bond', 'fluorine chlorine', 'fluorine bond', 'effect fluorine', 'oxygen' |
| **6** | **395** | **'caries', 'dental caries', 'dental', 'prevention', 'caries prevention', 'prevention dental', 'prophylaxis', 'prevention dental caries', 'fluorides', 'effect', 'caries prophylaxis', 'preventive', 'use', 'fluorosis', 'artificial', 'artificial caries', 'root', 'caries preventive', 'dental caries prevention', 'root caries'** |
| 7 | 466 | 'atoms', 'fluorine atoms', 'fluorine', 'substitution', 'fluorine substitution', 'reactions', 'reactions fluorine atoms', 'reactions fluorine', 'reaction', 'reaction fluorine atoms', 'substitution fluorine', 'reaction fluorine', 'aromatic', 'nucleophilic', 'effects fluorine', 'effects', 'oxygen', 'compounds', 'effects fluorine substitution', 'atom' |
| 8 | 1,233 | 'fluorine containing', 'containing', 'fluorine', 'synthesis', 'synthesis fluorine containing', 'synthesis fluorine', 'compounds', 'new', 'aromatic', 'new fluorine containing', 'new fluorine', 'polymers', 'derivatives', 'beta', 'properties', 'reaction', 'reactions', 'acids', 'containing polymers', 'fluorine containing polymers' |
| **9** | **157** | **'osteoporosis', 'fluorophosphate', 'treatment', 'treatment osteoporosis', 'di isopropyl', 'therapy', 'isopropyl', 'di isopropyl fluorophosphate', 'isopropyl fluorophosphate', 'therapy osteoporosis', 'di', 'sodium', 'bone', 'glaucoma', 'osteoporosis sodium', 'diisopropyl fluorophosphate', 'diisopropyl', 'postmenopausal', 'treatment glaucoma', 'postmenopausal osteoporosis'** |
| 10 | 352 | 'fluorine compounds', 'compounds', 'fluorine', 'organic', 'organic fluorine', 'elemental fluorine', 'organic fluorine compounds', 'elemental', 'studies organic', 'studies organic fluorine', 'organic compounds', 'fluorination', 'studies', 'using elemental', 'using elemental fluorine', 'synthesis', 'reactions', 'fluorine organic', 'chemistry organic', 'chemistry organic fluorine' |
| **11** | **768** | **'calcium', 'sodium', 'effect', 'effect sodium', 'phosphate', 'crystals', 'calcium phosphate', 'growth', 'effects', 'acid', 'monofluorophosphate', 'solution', 'study', 'bone', 'sodium monofluorophosphate', 'formation', 'calcium crystals', 'potassium', 'kinetics', 'effect calcium'** |
| 12 | 400 | 'electron', 'barium', 'fluorine', 'electron transfer', 'beam', 'electron beam', 'resonance', 'transfer', 'electron paramagnetic', 'paramagnetic', 'crystals', 'electron paramagnetic resonance', 'paramagnetic resonance', 'study', 'ions', 'electron diffraction', 'diffraction', 'lithium', 'spectra', 'pi' |
| **13** | **678** | **'enamel', 'dental', 'dental fluorosis', 'fluorosis', 'uptake', 'dental enamel', 'effect', 'surface', 'remineralization', 'tooth', 'plaque', 'lesions', 'surface enamel', 'concentration', 'application', 'acid', 'demineralization', 'study', 'caries', 'teeth'** |

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| 14 | 433 | 'rare', 'earth', 'rocks', 'rare earth', 'minerals', 'ree', 'rich', 'fluid', 'magmatic', 'elements', 'ore', 'fluorine', 'bearing', 'granite', 'melt', 'granites', 'deposits', 'hydrothermal', 'fluids', 'fluorite' |
| **15** | **335** | **'phase', 'gas phase', 'gas', 'fluorine', 'solid phase', 'solid', 'phase transfer', 'reactions', 'phase transitions', 'phase chronic', 'transfer', 'skeletal phase chronic', 'skeletal phase', 'phase transition', 'transitions', 'liquid', 'transition', 'synthesis', 'beta', 'containing'** |
| 16 | 520 | 'lithium', 'lif', 'thermoluminescent', 'response', 'thermoluminescence', 'dosimetry', 'dose', 'dosimeters', 'tld', 'energy', 'radiation', 'dosimeter', 'neutron', 'thermoluminescent dosimeters', 'lithium crystals', 'crystals', 'gamma', 'thermoluminescence lithium', 'thermal', 'thermoluminescent lithium' |
| 17 | 236 | 'fluorine chemistry', 'chemistry', 'fluorine', 'award', 'work fluorine', 'creative', 'work fluorine chemistry', 'acs', 'creative work fluorine', 'creative work', 'acs award', 'issue', 'preface', 'special issue', 'award creative work', 'award creative', 'work', 'special', 'acs award creative', 'chemistry fluorine' |
| **18** | **195** | **'fluoridated', 'fluoridated water', 'water', 'caries', 'milk', 'fluoridated milk', 'communities', 'apatites', 'non fluoridated', 'effect fluoridated', 'salt', 'fluoridated hydroxyapatites', 'hydroxyapatites', 'fluoridated salt', 'fluoridated area', 'fluoridated apatites', 'non', 'dental', 'effect', 'nonfluoridated'** |
| 19 | 374 | 'aluminum', 'content', 'fluorine content', 'fluorine', 'water', 'teas', 'waters', 'content water', 'effect', 'cryolite', 'foods', 'bottled', 'sodium', 'kinetics', 'effects', 'content bottled', 'acid', 'sodium aluminum', 'magnesium', 'molten' |
| **20** | **161** | **'topical', 'topical application', 'application', 'topical applications', 'enamel', 'applications', 'uptake', 'topical agents', 'caries', 'effect topical', 'effect', 'topical treatment', 'agents', 'stannous', 'treatment', 'dental', 'plaque', 'following', 'solutions', 'following topical'** |
| 21 | 382 | 'properties', 'properties fluorine', 'thermodynamic properties', 'thermodynamic', 'fluorine', 'physical', 'physical properties', 'effect', 'production streptococcus', 'production streptococcus mutans', 'structure properties', 'structure', 'streptococcus', 'sodium', 'production', 'magnetic properties', 'containing', 'properties sodium', 'preparation properties', 'influence' |
| 22 | 541 | 'solutions', 'chloride', 'aqueous', 'aqueous solutions', 'melts', 'extraction', 'chloride melts', 'niobium', 'ammonium', 'tantalum', 'phosphate', 'exchange', 'anion', 'potassium', 'bromide', 'titanium', 'uranium', 'iv', 'sodium', 'ion' |
| 23 | 560 | 'ion', 'reactions', 'fluorine ion', 'involving ion', 'reactions involving ion', 'reactions involving', 'fluorine', 'involving', 'ion induced', 'presence ion', 'induced', 'ions', 'effect', 'ion implantation', 'presence', 'implantation', 'study', 'exchange', 'effect ion', 'ion exchange' |
| 24 | 156 | 'graphite', 'intercalation', 'graphite intercalation', 'intercalation compounds', 'compounds', 'fluorine', 'graphite intercalation compounds', 'intercalated', 'intercalation compound', 'preparation', 'fluorine graphite', 'graphite intercalation compound', 'intercalated graphite', 'fluorine intercalated graphite', 'fluorine intercalated', 'compound', 'graphite compounds', 'conductivity', 'electrical', 'preparation graphite' |
| **25** | **9,479** | **'effect', 'synthesis', 'new', 'reaction', 'using', 'study', 'effects', 'polyvinylidene', 'structure', 'compounds', 'studies', 'reactions', 'activity', 'formation', 'containing', 'analysis', 'based', 'acid', 'high', 'use'** |

**Bold font** indicates topic clusters that appear to include studies that meet the populations, exposures, comparators, and outcomes (PECO) criteria based on the listed terms or included studies identified in the crosswalk with published assessments. N = 12,725 studies.

**Table B-7. Targeted Topic Extraction Results for Fluoride Literature with No Tag in SWIFT-Review from Cluster 25 of Targeted Topic Extraction of Clusters 3, 12, and 14**

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| 1 | 140 | ['stability', 'chromyl', 'thermal', 'thermal stability', 'fluorine', 'chemistry chromyl', 'containing', 'formation', 'synthesis', 'apatites', 'metal stability', 'effect', 'cro2f2', 'stability toothpastes', 'concentration stability', 'chemistry', 'stability chromyl', 'influence', 'study', 'new'] |
| **2** | **446** | **['mutans', 'streptococcus', 'streptococcus mutans', 'formation', 'glass', 'production', 'ph', 'development', 'results', 'study', 'caries', 'interaction', 'effect', 'action', 'biofilm', 'acid', 'cariogenic', 'release', 'inhibition', 'old']** |
| 3 | 431 | ['reaction', 'methyl', 'solvent', 'solvents', 'mediated', 'tetramethylammonium', 'organic', 'effect', 'potassium', 'reactions', 'organic solvents', 'fluorine', 'using', 'conditions', 'products', 'proton', 'study', 'formation', 'substitution', 'basic'] |
| 4 | 427 | ['chemistry', 'exchange', 'using', 'vi', 'sulfonyl', 'free', 'silica', 'sufex', 'salts', 'conditions', 'click', 'reagents', 'new', 'reaction', 'reactions', 'synthesis', 'sulfur', 'syntheses', 'substituted', 'catalysts'] |
| 5 | 256 | ['gas', 'sulfur', 'carbon', 'diffusion', 'mixtures', 'dioxide', 'sulfur hexafluoride', 'hexafluoride', 'emissions', 'liquid', 'gases', 'sf6', 'sulfur dioxide', 'reaction', 'gas liquid', 'chromatography', 'carbon dioxide', 'analysis', 'greenhouse', 'using'] |
| **6** | **355** | **['effect', 'hydroxyapatite', 'growth', 'kinetics', 'crystal', 'bone', 'uptake', 'apatite', 'crystal growth', 'stannous', 'crystals', 'plaque', 'uptake hydroxyapatite', 'activity', 'surface', 'ph', 'dissolution', 'dentifrice', 'mechanism', 'salivary']** |
| **7** | **524** | **['studies', 'enzyme', 'mechanism', 'binding', 'site', 'substrate', 'glucose', 'enzymes', 'active', 'molecular', 'inhibition', 'active site', 'experimental', 'inhibitors', 'oxidase', 'cytochrome', 'activity', 'protein', 'irreversible', 'reaction']** |
| 8 | 357 | ['infrared', 'based', 'spectroscopy', 'detection', 'pressure', 'strength', 'trace', 'analysis', 'study', 'transitions', 'double', 'using', 'atmospheric', 'ir', 'identification', 'methyl', 'used', 'power', 'spectroscopic', 'fluorine'] |
| 9 | 320 | ['systems', 'spectra', 'containing', 'vibrational', 'raman', 'vibrational spectra', 'infrared', 'silicate', 'raman spectra', 'studies', 'study', 'evaluation', 'effect', 'synthesis', 'infrared spectra', 'new', 'spectroscopy', 'temperature', 'formation', 'water'] |
| 10 | 147 | ['characterization', 'applications', 'film', 'synthesis', 'synthesis characterization', 'polyvinylidene', 'oriented', 'polyvinylidene film', 'new', 'transducer', 'sensor', 'preparation characterization', 'preparation', 'talk applications', 'films', 'poly', 'polyvinyl', 'talk', 'n3nfo', 'chemical'] |
| **11** | **307** | **['effects', 'oral', 'health', 'oral health', 'oral bacteria', 'dental', 'hygiene', 'stannous', 'bacteria', 'public', 'oral hygiene', 'plaque', 'public health', 'streptococci', 'use', 'oral streptococci', 'effect', 'exposure', 'care', 'dental health']** |
| 12 | 165 | ['polyvinylidene', 'pyroelectricity', 'pyroelectricity polyvinylidene', 'piezoelectricity', 'piezoelectricity pyroelectricity polyvinylidene', 'piezoelectricity pyroelectricity', 'films', 'polyvinylidene films', 'pyroelectric', 'hysteresis', 'effect polyvinylidene', 'crystallization polyvinylidene', 'pvf2', 'transducers', 'crystallization', 'corona', 'polyvinylidene pvf2', 'effect', 'currents polyvinylidene', 'polarization'] |
| **13** | **721** | **['reactions', 'new', 'compounds', 'activity', 'group', 'fluorine', 'containing', 'synthesis', 'rights reserved', 'rights', 'reserved', 'derivatives', 'science', 'inhibitors', 'active', 'fluorine containing', 'anions', 'reaction', 'synthesized', 'structure']** |
| 14 | 451 | ['magnesium', 'oxide', 'preparation', 'compounds', 'technique', 'low', 'adsorption', 'new', 'potassium', 'using', 'reaction', 'structure', 'synthesis', 'method', 'high', 'use', 'temperature', 'strength', 'windows', 'study'] |
| 15 | 247 | ['synthesis', 'ionic', 'ionic conductivity', 'conductivity', 'liquids', '10', 'article', 'potassium', 'nanoparticles', 'ionic liquids', 'carbonate', 'metal', 'butyl', 'doi', 'doi 10', 'new', 'precursors', 'using', 'upconverting', 'upconverting nanoparticles'] |

| Topic Cluster | Number of References | Keywords/Topic Signature |
|---|---|---|
| **16** | **88** | **['silver', 'diamine', 'diammine', 'silver diamine', 'ag', 'diammine silver', 'reaction', 'diffusion silver', 'polymorphism silver', 'structure silver', 'diamine diammine', 'reaction silver', 'ii', 'teeth', 'polymorphism', 'silver nitrate', 'dental', 'sdf', 'diamine silver', 'detection formation']** |
| **17** | **110** | **['addition', 'sealants', 'fissure', 'fissure sealants', 'pit fissure', 'pit', 'release', 'pit fissure sealants', 'strength', 'sealant', 'michael', 'effect', 'michael addition', 'bond', 'varnish', 'radical', 'molars', 'permanent molars', 'unsaturated', 'addition bromine']** |
| 18 | 367 | ['fluorination', 'recent', 'review', 'bonds', 'selective', 'fluorine', 'synthesis', 'years', 'strategies', 'reactivity', 'organic', 'advances', 'synthetic', 'recent advances', 'applications', 'sources', 'reactions', 'electrophilic', 'direct', 'molecules'] |
| **19** | **169** | **['release', 'protease', 'enzyme', 'serine', 'purified', 'activity', 'inhibited', 'ph', 'phenylmethylsulfonyl', 'purification', 'kda', 'gel', 'orthodontic', 'serine protease', 'extracellular', 'degrees', 'inhibitor', 'bonding', 'chromatography', 'molecular']** |
| 20 | 257 | ['acids', 'lewis', 'acid', 'lewis acids', 'lewis acid', 'difference', 'acidity', 'lewis acidity', 'reaction', 'formation', 'boron', 'carboxylic acids', 'carboxylic', 'bidentate', 'amino acids', 'amino', 'synthesis', 'acidic', 'based', 'fluorinated'] |
| 21 | 487 | ['analysis', 'metal', 'structure', 'interactions', 'role', 'function', 'coordination', 'compounds', 'fluorine', 'chemistry', 'new', 'alkaline', 'developments analysis', 'synthesis', 'alkali', 'alkali metal', 'transition', 'using', 'molecular', 'reactions'] |
| **22** | **2,009** | **['reply', 'study', 'toothpaste', 'intake', 'bone', 'fluoridation', 'use', 'toxicity', 'treatment', 'concentration', 'teeth', 'uptake', 'dentifrices', 'levels', 'plaque', 'toothpastes', 'dentifrice', 'potassium', 'evaluation', 'concentrations']** |
| 23 | 52 | ['research', 'international', 'society', 'society research', 'international society', 'conference', 'international society research', 'conference international society', 'conference international', 'abstracts', 'papers', 'abstracts papers', 'papers presented', 'september', 'abstracts papers presented', 'recent', 'international research', 'presented', 'report', '2018'] |
| **24** | **343** | **['metabolism', 'alpha', 'high', 'mass', 'beta', '15', 'synthesis', 'chain', '14', 'derivatives', '13', 'incorporation', 'nmr', 'analyses', 'deuterium', 'prepared', 'activities', '19', 'reaction', '23']** |
| **25** | **303** | **['materials', 'dentin', 'acid', 'potential', 'restorative materials', 'restorative', 'form', 'resistant', 'containing', 'layer', 'release', 'treatment', 'effect', 'releasing', 'treated', 'resistance', 'surface', 'root', 'root dentin', 'synthesis']** |

**Bold font** indicates topic clusters that appear to include studies that meet the populations, exposures, comparators, and outcomes (PECO) criteria based on the listed terms or included studies identified in the crosswalk with published assessments. N = 5,375 studies.

## B.2.3. Title-abstract Screening

Upon completion of SWIFT-Review filtering and additional prioritization steps, the literature search results were imported into SWIFT-Active Screener (Howard et al., 2020) and the studies were screened using the initial problem formulation PECO criteria (Table B-2) at the title and abstract level to identify relevant studies. In total, 74,102 studies were forwarded for title-abstract screening in SWIFT-Active Screener. Title-abstract screening was performed by two independent screeners in SWIFT-Active Screener. If results from the two independent screeners conflicted, the conflict was resolved by a senior-level tertiary screener. The machine learning component of SWIFT-Active Screener was used to predict relevant references and expedite the screefning of fluoride. Studies were screened until the algorithm predicted that 95% of the relevant studies had been screened and included (95% threshold). Studies that reported mechanistic data (including *in vitro* studies) were also included and tracked as supplemental during title-abstract screening to ensure that they were prioritized by SWIFT-Active Screener's machine learning model.

## B.2.4. Prioritization Following Title-abstract Screening

Additional prioritization was conducted following title-abstract screening and prior to full-text screening. Priority health outcomes identified during problem formulation (see Section 2.2) were used to refine the scope for full-text screening.

Studies examining neurodevelopmental and dental effects that were considered for dose-response assessment in existing assessments were prioritized for full-text screening. Five existing assessments were reviewed to identify these studies: EPA's Fluoride: Dose-Response Analysis for Non-Cancer Effects – Dental Fluorosis: Evaluations of Key Studies (U.S. EPA, 2008a) and Dose-Response Analyses (U.S. EPA, 2010a); Health Canada's 2010 Guidelines for Drinking Water (Health Canada, 2010); Taher et al. (2024); and the EFSA Scientific Opinion from 2025 (EFSA Scientific Committee, 2025). Additionally, although dose-response was not conducted as part of the assessment, neurodevelopment studies from the 2024 NTP Monograph (NTP, 2024) were also prioritized for full-text screening. After review and deduplication of the dose-response studies from these assessments, 193 studies were forwarded for full-text screening.

For the remaining studies, SWIFT-Review filtering (see Section B.2.2.1) was used to apply tags corresponding to the health effects examined in each title and abstract. Health outcome search strings (including for cancer and nervous system effects) are publicly available on the Sciome webpage and can be used to conduct such tagging in SWIFT-Review; however, custom strings were also developed to generate project-specific health outcome tags. The existing cancer search string in SWIFT-Review was used to tag studies reporting cancer findings. The existing nervous system string was refined to target neurodevelopmental effects via expert consultation and review of strings used in previous assessments (e.g., the NTP (2024)). A new string was developed to identify dental effects. All string development occurred in consultation with experts. To validate the new strings, references from existing assessments with known health outcomes (e.g., neurodevelopment for the 2024 NTP Monograph (NTP, 2024) and dental effects from the 2008 EPA dose-response assessments (U.S. EPA, 2008a)) were tagged via SWIFT-Review.

Along with health outcome tagging, studies were tagged to evidence streams (see Section B.2.2.1) to prioritize human and animal studies for screeners with appropriate expertise.

Following the development and validation of the dental and neurodevelopmental strings, all studies included during title-abstract screening (n = 6,580) underwent SWIFT-Review filtering for health outcome and evidence stream tagging (Table B-8). Given the large number of studies tagged to "Human" and "Dental" tags, a subset of studies tagged to the "Epidemiological Quantitative Analysis" and "Dental" tags was identified.

**Table B-8. SWIFT-Review Filtering Results for Health Outcome and Evidence Stream**

| Evidence Stream[a,b] | Total | Human | Animal | No Evidence Stream Tag |
|---|---|---|---|---|
| Health Outcome[c] | 6,580 (100%) | 4,917 (75%) | 2,442 (37%) | 558 (8%) |
| Dental | 4,377 (67%) | 3,736 (76%) | 1,530 (63%) | 207 (37%) |
| Neurodevelopmental | 297 (5%) | 205 (4%) | 164 (7%) | 4 (1%) |
| Cancer | 217 (3%) | 144 (3%) | 108 (4%) | 9 (2%) |
| No Priority Health Outcome Tag | 2,413 (37%) | 1,362 (27%) | 1,024 (42%) | 353 (63%) |

[a] Studies may receive more than one health outcome or evidence stream tag, which may lead to percentages not adding to 100%.
[b] The percentage of studies with each evidence stream tag is determined from the overall total number of references tagged in Swift-Review (n = 6,580).
[c] The percentage of studies within each health outcome category is determined by the number of studies tagged to each specific evidence stream noted in the column title.

After removing the 193 dose-response studies already forwarded for full-text screening and overlaps between tags, studies from the following groups were prioritized:

- Human – Neurodevelopmental (n = 116)
- Human – Cancer (n = 44)
- Epi Quantitative Analysis – Dental (n = 2,219)
- Animal – Cancer (n = 67)
- Select No Tag Priority Studies (n = 40)
- Animal-Neurodevelopmental (n = 62)

After manually screening over 1,000 studies in the Epi Quantitative Analysis – Dental category at the full-text level (see Section B.2.5) and identifying only 25 relevant dental studies with sufficient quantitative information for dose-response, additional prioritization options were explored for this subset of studies. First, titles and abstracts from the studies tagged to Epi Quantitative Analysis – Dental and dental studies that received only the Human evidence tag ("Human – Dental") (n = 1,306) were compared to confirm if the studies with Epi Quantitative Analysis tags were more likely to provide data for dose-response modeling. After review, the studies in both tagging groups appeared to be similar, and it was determined that Human – Dental studies should also undergo full-text screening. Additional prioritization was conducted to 1) prioritize the remaining Epi Quantitative Analysis – Dental studies to identify those most likely to provide data for dose-response analyses, and 2) prioritize all Human – Dental studies to identify those most likely to be relevant and provide data for dose-response analyses.

Supervised clustering (see Section B.2.2.2) was used to prioritize the remaining dental studies for full-text screening. The 25 Epi Quantitative Analysis – Dental studies identified as relevant and having sufficient quantitative data for dose-response modeling during initial full-text screening

were used as positive seed studies to predict the remaining dental studies most likely to be relevant. The approach was tested using all Epi Quantitative Analysis – Dental studies that had successfully undergone PDF retrieval (n = 786). Of these 786 studies, 336 had been screened by the time the prioritization test was conducted. Results from screening were mapped to supervised clustering results to identify where studies that were relevant and provided sufficient quantitative data fell. The results from this test are provided in brief in Table B-9 and confirmed that this approach could be used to identify studies most likely to be informative for the assessment (i.e., percent of studies of interest increased with each increasing ensemble score).

**Table B-9. Results from Supervised Clustering Approach to Identify Relevant Dental Studies with Information for Dose-Response Modeling**

| Ensemble Score | Count of Studies in Ensemble Score (includes seed studies) | Percent of Relevant Studies with Sufficient Data (%) |
|---|---|---|
| 0 | 434 | 1.1 |
| 1 | 99 | 9.3 |
| 2 | 81 | 14.3 |
| 3 | 98 | 22.2 |
| 4 | 48 | 25.8 |
| 5 | 43 | 25.9 |
| 6 | 8 | 60 |
| **Grand Total** | **811** | |

After validating the approach, the remaining studies tagged to Epi Quantitative Analysis – Dental that had not been screened at the full-text level (n = 712) underwent supervised clustering using the 25 dental seed studies. Results are provided in Table B-10. Studies that received ensemble scores 1–6 moved forward for full-text screening and literature inventory (n = 193 unique new studies), bringing the total number of Epi Quantitative – Dental studies for full-text screening to 1,701.

**Table B-10. Results from Supervised Clustering of Epi Quantitative Analysis – Dental Studies Awaiting Full-Text Screening**

| Ensemble Scores | Number of Studies | Number of Seed Studies |
|---|---|---|
| 0 | 519 | 0 |
| 1 | 72 | 1 |
| 2 | 33 | 2 |
| 3 | 29 | 0 |
| 4 | 35 | 1 |
| 5 | 32 | 9 |
| 6 | 17 | 12 |
| **Grand Total** | **737** | **25** |

Additionally, all unique studies tagged to Human – Dental (i.e., those that did not also receive the Epi Quantitative Analysis tag) underwent supervised clustering using the same 25 dental seed studies. None of the 1,306 studies had been screened at the full-text level. Results are in Table B-11. Studies that received ensemble scores 1–6 moved forward for full-text screening and literature inventory (n = 317 unique new studies).

**Table B-11. Results from Supervised Clustering of Human – Dental Studies Awaiting Full-Text Screening**

| Ensemble Scores | Number of Studies | Number of Seed Studies |
|---|---|---|
| 0 | 989 | 0 |
| 1 | 178 | 1 |
| 2 | 71 | 0 |
| 3 | 33 | 2 |
| 4 | 18 | 8 |
| 5 | 24 | 10 |
| 6 | 18 | 4 |
| **Grand Total** | **1,331** | **25** |

## B.2.5. Full-text Screening and Literature Inventory

Records that were not excluded based on title and abstract were then screened at the full-text level according to the refined PECO criteria (Table 4-1) using ICF's Litstream™ software. Full-text copies of the records were retrieved and stored in EPA's HERO database. Studies meeting the refined PECO criteria were tagged as included and were briefly summarized in Litstream to capture information on study design, study populations, exposure measurement information, studied health outcomes, and whether the study reports quantitative data with sufficient detail to potentially support dose-response analysis. Studies that met the problem formulation PECO but did not meet refined PECO criteria were tagged but did not undergo literature inventory extraction, except for studies reporting on the development of cancer following fluoride exposure (see Appendix C). A primary reviewer completed the initial screening and literature inventory (if applicable), and all studies underwent secondary review for quality assurance by a senior reviewer.

# Appendix C. Cancer Literature Inventory

During full-text screening, 23 epidemiology studies and four animal toxicology studies were identified that met problem formulation PECO criteria (Appendix B, Table B-2) and that reported on the association between fluoride exposure and cancer. These studies were briefly summarized in Litstream to capture information on study design, study populations, exposure measurement information, and health outcomes, as well as a summary of results and author-reported statistical significance. Based on the literature inventory results, EPA determined that reassessment of carcinogenicity with the current dataset would be unlikely to yield a different conclusion from the existing published cancer assessments (Table 2-2).

## C.1. Epidemiological Data on Cancer

The literature inventory of epidemiology study designs and health systems assessed for cancer following fluoride exposure is summarized in Figure C-1. An interactive dashboard is available at: https://public.tableau.com/views/FluorideCancerSEM_17676390993130/Humanevidence?:language=en-US&:sid=&:redirect=auth&:display_count=n&:origin=viz_share_link. Of the 23 studies identified in EPA's literature search, 19 have been previously evaluated in the published assessments of fluoride carcinogenicity by authoritative agencies (Table 2-2). The weight of the evidence across these 19 studies, which included a variety of geographic regions worldwide and assessed exposures and outcomes across a range of lifestages and study designs, does not support an association between fluoride exposure and carcinogenicity. The limitations of some of these epidemiological data have been reviewed previously (NRC, 2006).

The four epidemiological studies that were not included in published assessments (Table C-1) reported inverse and null results for osteosarcoma, eye cancers, and cancer mortality. These four studies do not provide evidence of a positive association between fluoride and cancer and are therefore unlikely to modify the previous cancer conclusions.

| Health System | Cancer Subtype | Cancer Metric | | Total Distinct References |
|---|---|---|---|---|
| | | Incidence | Mortality | |
| All sites | All sites | 1 | 5 | 6 |
| Blood | Leukemia | | 1 | 1 |
| Dermal | Skin | | 1 | 1 |
| Endocrine | Breast | 1 | 1 | 2 |
| | Pancreas | | 2 | 2 |
| | Thyroid | 1 | | 1 |
| Gastrointestinal | Colon/Intestine | 1 | 3 | 4 |
| | Digestive organs and peritoneum | | 1 | 1 |
| | Esophagus | 1 | 3 | 4 |
| | Oral cavity and pharynx | | 2 | 2 |
| | Rectum | 1 | 3 | 4 |
| | Stomach | 1 | 3 | 4 |
| Hepatic | Liver | | 1 | 1 |
| Muskuloskeletal | Bone | 3 | 1 | 4 |
| | Ewing sarcoma | 1 | | 1 |
| | Osteosarcoma | 12 | | 12 |
| | Secondary bone cancer | 1 | | 1 |
| Nervous | Brain | | 1 | 1 |
| Ocular | Eye and orbit | 1 | | 1 |
| Renal/Urinary | Bladder | 2 | 3 | 5 |
| | Bladder/Kidney | | 1 | 1 |
| | Kidney | 1 | 3 | 4 |
| Reproductive | Breast | | 3 | 3 |
| | Cervix/Uterus | | 2 | 2 |
| | Genital | | 1 | 1 |
| | Ovary | | 3 | 3 |
| | Prostate | | 1 | 1 |
| Respiratory | Lung | | 2 | 2 |
| | Respiratory | | 1 | 1 |
| Other | Other malignant neoplasms | | 1 | 1 |
| **Total Distinct References** | | 16 | 7 | 23 |

**Figure C-1. Survey of Epidemiology Studies Evaluating the Association Between Fluoride Exposure and Cancer, With Cancer Subtype and Metric Evaluated**

The numbers indicate the number of studies that investigated a particular topic, not the number of studies that observed an association with fluoride exposure. If a study evaluated cancer subtypes or metrics of exposure, it is shown here multiple times.

**Table C-1. Summary of Four Epidemiological Studies Not Previously Included in Published Fluoride Toxicity Assessments from the Authoritative Sources Listed in Table 2-2**

| Reference | Study Design | Outcomes Assessed | Results Overview | Summary |
|---|---|---|---|---|
| Schwartz (2014) | Ecological | Eye and orbit cancers (proxy for uveal melanoma) | Eye cancer rates (all ages) inversely correlated with percent of the population with access to fluoridated water | Inverse association |
| Levy and Leclerc (2012) | Ecological | Osteosarcoma | No significant difference when comparing child and adolescent cancer rates between communities with high versus low fluoride | Null results |
| (Comber et al., 2011) | Ecological | Osteosarcoma | No significant difference when comparing standardized rate ratios in fluoridated versus non-fluoridated areas (including in sub-analyses by age and sex). | Null results |
| Richards and Ford (1979) | Ecological | Cancer mortality | No significant difference when comparing cancer standardized mortality ratios for communities of fluoride vs. non-fluoride water supplies | Null results |

## C.2. Animal Toxicological Data on Cancer

Four publications describe the incidence of neoplastic lesions in rats and mice exposed for up to two years to sodium fluoride in drinking water (NTP, 1992, 1990) or diet (Maurer et al., 1993; Maurer et al., 1990). These studies were identified by EPA's literature search and are all included in the previously published assessments of fluoride carcinogenicity (Table 2-2). The literature inventory of animal study designs and health systems assessed for cancer is summarized in Figure C-2. An interactive dashboard is available at: https://public.tableau.com/views/FluorideCancerSEM_17676390993130/Animalevidence?:language=en-US&:sid=&:redirect=auth&:display_count=n&:origin=viz_share_link

As reviewed previously by NRC (2006), these studies either do not support an association between fluoride exposure and carcinogenicity or provide equivocal evidence[4] about the relationship between fluoride exposure and carcinogenicity.

[4] The NTP (1990) study concluded that there was equivocal evidence of carcinogenicity for male rats based on incidences of 1/50 in the second highest dose group as well as 3/80 in the highest dose group for bone osteosarcoma, which is a rare tumor in rats. The finding of dose-responsive osteosarcoma was not replicated in a subsequent study of sodium fluoride in male rats (NTP, 1992). There was no evidence of carcinogenicity for female rats, male mice, and female mice in the NTP 1990 study.

| | | Species and Exposure Route | | | | |
|---|---|---|---|---|---|---|
| | | Mouse | | Rat | | |
| **Health System** | **Tissue** | Diet | Drinking water | Diet | Drinking water | **Total Distinct References** |
| Cardiovascular | Blood vessel | | 1 | | | 1 |
| | Heart | | 1 | 1 | 1 | 2 |
| Dental | Tooth | 1 | 1 | 1 | 2 | 4 |
| Endocrine | Adrenal gland | | 1 | 1 | 2 | 3 |
| | Pancreas | | 1 | 1 | 1 | 2 |
| | Parathyroid | | 1 | 1 | 1 | 2 |
| | Pituitary | | 1 | 1 | 1 | 2 |
| | Thyroid | | 1 | 1 | 1 | 2 |
| Gastrointestinal | Gallbladder | | 1 | | 1 | 1 |
| | Large intestine | | 1 | | 1 | 1 |
| | Mesentery | | 1 | | 1 | 1 |
| | Oral mucosa | | | | 2 | 2 |
| | Pancreas | | 1 | 1 | 1 | 2 |
| | Pharynx | | | | 1 | 1 |
| | Salivary glands | | 1 | | 1 | 1 |
| | Small intestine | | 1 | | 1 | 1 |
| | Stomach | | 1 | 1 | 1 | 2 |
| | Tongue | | | | 1 | 1 |
| General/Systemic | Multiple organs | | 1 | | 2 | 2 |
| | Tissue not otherwise specified | | | | 2 | 2 |
| Hematopoietic | Blood | | 1 | | | 1 |
| | Bone marrow | | 1 | | 2 | 2 |
| Hepatic | Liver | | 1 | 1 | 1 | 2 |
| Immune | Lymph node | | 1 | | 1 | 1 |
| | Spleen | | 1 | 1 | 1 | 2 |
| | Thymus | | 1 | | 1 | 1 |
| Musculoskeletal | Bone | 1 | 1 | 1 | 2 | 4 |
| | Skeletal muscle | | 1 | | 1 | 1 |
| Nervous System | Brain | | 1 | 1 | 1 | 2 |
| | Spinal cord | | | 1 | 1 | 2 |
| Renal/Urinary | Bladder | | 1 | 1 | 1 | 2 |
| | Kidney | | 1 | 1 | 1 | 2 |
| | Ureter | | 1 | | | 1 |
| Reproductive | Cervix | | | | 1 | 1 |
| | Clitoral gland | | 1 | | 1 | 1 |
| | Epididymis | | 1 | 1 | 1 | 2 |
| | Mammary gland | | 1 | | 1 | 1 |
| | Ovary | | 1 | 1 | 1 | 2 |
| | Preputial gland | | 1 | | 1 | 1 |
| | Prostate | | 1 | 1 | 1 | 2 |
| | Seminal vesicle | | 1 | 1 | 1 | 2 |
| | Testes | | 1 | 1 | 1 | 2 |
| | Uterus | | 1 | 1 | 1 | 2 |
| | Vagina | | | | 1 | 1 |
| Respiratory | Lung | | 1 | 1 | 1 | 2 |
| | Nose | | 1 | | 1 | 1 |
| Skin | Skin | | 1 | | 1 | 1 |
| Special Senses | Ear | | 1 | | 1 | 1 |
| | Eye | | | | 1 | 1 |
| | Harderian gland | | 1 | | 1 | 1 |
| | Zymbal's gland | | | | 1 | 1 |
| **Total Distinct References** | | 1 | 1 | 1 | 2 | 4 |

**Figure C-2. Survey of Animal Studies Evaluating the Association Between Fluoride Exposure and Cancer, With Exposure Route and Tissue Types Evaluated**

The numbers indicate the number of studies that investigated a particular topic, not the number of studies that observed an association with fluoride exposure. If a study evaluated multiple tissues or study designs, it is shown here multiple times.

# Appendix D. Preliminary Literature Flow Diagram

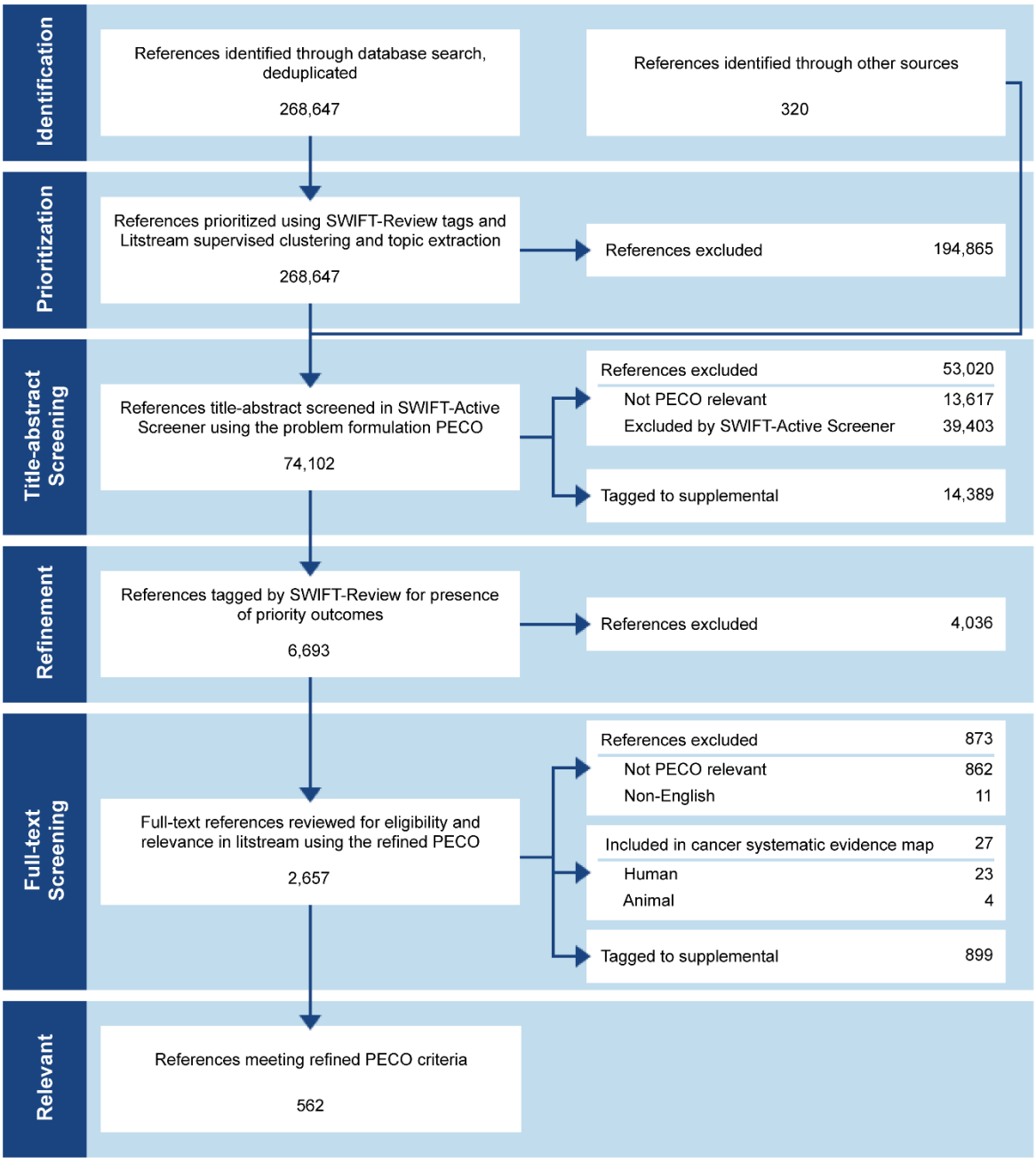


**Figure D-1. Literature Survey Study Flow Selection Diagram for Fluoride Toxicity Assessment**

PECO = populations, exposures, comparators, and outcomes.
The numbers reported in the study flow selection diagram represent the systematic review steps performed to date and are current as of January 12, 2026. Systematic review work is ongoing. "Other sources" include studies identified from assessments published by other agencies. An interactive dashboard is available at: https://public.tableau.com/app/profile/ow.hecd.visuals/viz/LiteratureSurveyforPreliminaryFluorideAssessmentPlan/LitFlow.