

July 11, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-N-1557—Use of Orally Ingestible Unapproved Prescription
Drug Products Containing Fluoride in the Pediatric Population

To Whom It May Concern:

As the leading authority on oral health in the United States, the American Dental Association (ADA), representing more than 159,000 dentists nationwide, submits the following comments in response to the request for input on the use of orally ingestible unapproved prescription drug products containing fluoride in the pediatric population, as outlined in the Federal Register notice of June 16, 2025 (90 FR 25329).

The FDA has empaneled the Reagan-Udall Foundation to develop a report on the many perspectives about the safety of prescription-strength fluoride supplements, with an emphasis on neurodevelopment and IQ scores, the gut microbiome, and thyroid function. These perspectives will be debated by researchers and advocates at a July 23 meeting.

Our detailed comments are provided in six parts, based on the above-mentioned *Federal Register* notice and the FDA's press release of May 13, 2025. You will find that the plurality of generally accepted scientific evidence does not support the hypothesis that fluoride ingestion is harmful, certainly not at recommended levels of exposure.

- [Attachment A](#)—Are fluoride supplements effective in helping to prevent tooth decay?
- [Attachment B](#)—When and how do dentists prescribe fluoride supplements?
- [Attachment C](#)—Does fluoride ingestion affect neurodevelopment and IQ scores?
- [Attachment D](#)—Does fluoride ingestion affect the gut microbiome?
- [Attachment E](#)—Does fluoride ingestion affect thyroid function?
- [Attachment F](#)—Are other health claims about fluoride ingestion justified?

The ADA welcomes the opportunity to assist the Reagan-Udall Foundation and the FDA with its review of scientific evidence, which includes sharing the best available scientific literature examining the safety of all fluoride-containing oral health products. It also includes providing access to independent peer reviewers with intimate knowledge about the strengths and weaknesses of the current literature.

Additionally, we would be pleased to share the latest edition of our compendium of answers to frequently asked questions about the safety, health benefits, and cost-effectiveness of not only community water fluoridation, but all sources of fluoride. Our goal in developing this

document, *Fluoridation Facts*, is to provide clear, well-cited answers to help policy makers and the public navigate the many myths and misperceptions about fluoride exposure(s).

Fluoridation Facts explores the symbiotic relationship between all fluoride-containing sources, including community water fluoridation; fluoride toothpastes and rinses; professionally applied fluoride foams, gels, and varnish; and prescription-strength supplements. You will find that use of these products is not an either/or proposition. Rather, they work in concert to prevent tooth decay and improve oral health in a safe, comprehensive, and time-tested manner.

Again, we would welcome the opportunity to explore how the ADA can partner with FDA on a review of prescription-strength fluoride supplements. In the meantime, we urge you to prioritize high-quality studies that are consistent with the review standards of the National Academies of Science, Engineering and Medicine, and other reputable scientific organizations—and discount literature that does not meet that standard.

Thank you for providing the opportunity to comment. If you have any questions, comments or require additional information, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/

Brett Kessler, D.D.S.
President

/s/

Elizabeth Shapiro, D.D.S., J.D., C.A.E.
Interim Executive Director

BHK:EAS:rjb
Enclosures (6)

ATTACHMENT A

EFFECTIVENESS OF FLUORIDE SUPPLEMENTS IN PREVENTING TOOTH DECAY

For patients who do not have regular access to recommended levels of fluoride, prescription-strength fluoride supplements can be vital option to help them maintain good oral health. The age of the patient, the fluoride content in local drinking water, and other factors will drive dentist’s decision about whether to recommend (or not recommend) fluoride supplements.

Dietary fluoride supplements are available only by prescription in the United States and are recommended by the ADA¹ and the US Preventive Services Task Force.^{2,3} They are recommended by the ADA for use by children who are at high risk for developing tooth decay and living in areas where the primary source(s) of water are deficient in fluoride.¹ Similar to the benefits of community water fluoridation, fluoride in dietary supplements is incorporated into developing teeth to strengthen them and reduce the risk of decay.²

Dietary fluoride supplements can be effective in helping to prevent tooth decay for those at high risk for tooth decay. To receive the optimal benefit from fluoride supplements, the use of supplements should begin at 6 months of age and continue daily until the child is 16 years old.¹

Recommendations for health professionals seeking to prescribe dietary fluoride supplements are found in *The Evidence-Based Clinical Recommendations on the Prescription of Dietary Fluoride: A Report of the American Dental Association Council on Scientific Affairs* published in 2010.¹ The *Chairside Guide: Dietary Fluoride Supplements: Evidence-Based Clinical Recommendations* can be accessed from the ADA’s website, ADA.org.⁴

The current dietary fluoride supplement schedule appears in Table A-1.

Table A-1. Dietary Fluoride Supplement Schedule for Children at High Caries Risk ¹			
Age	Fluoride ion level in drinking water (ppm)*		
	<0.3 mg/L	0.3-0.6 mg/L	>0.6 mg/L
Birth-6 months	None	None	None
6 months-3 years	0.25 mg/day**	None	None
3-6 years	0.50 mg/day	0.25 mg/day	None
6-16 years	1.0 mg/day	0.50 mg/day	None
* 1.0 part per million (ppm) = 1 milligram/liter (mg/L).			
** 2.2 mg sodium fluoride contains 1 mg fluoride ion.			

The expert panel convened by the ADA Council on Scientific Affairs developed the recommendations and emphasized that they must be balanced with the practitioner’s professional judgment and the individual patient’s needs and preferences. They also emphasized that children are exposed to multiple sources of fluoride. The panel encouraged health care providers to evaluate all potential fluoride sources and to conduct a caries risk assessment before prescribing systemic fluoride supplements.

Specific to prescribing dietary fluoride supplements, the recommendations included conducting an accurate assessment of the fluoride content of the patient’s primary drinking water source(s).¹ The identification of the “primary” sources is sometimes difficult because some patients have multiple

sources of drinking water during a typical day. For example, while a patient may have access to drinking water in the home, they often also spend a large part of their day accessing drinking water at day care, school, or a place of work, which could be a different water system. To determine fluoride levels, it might be necessary to contact the local, county, or state health departments or municipalities or private water companies for information on the fluoride content of multiple public water sources or to contact a certified laboratory that can provide a fluoride test for private wells.

The ADA offers information on caries risk assessment⁵ on its website. Caries risk assessments should be completed for patients on a regular basis to determine their risk for tooth decay, which can change over time.

While dietary fluoride supplements can be an effective means of caries prevention, they must be used daily, and individual patterns of adherence to the schedule (compliance) vary greatly. Therefore, the recommendations suggest that providers carefully monitor compliance to maximize the therapeutic benefit of dietary fluoride supplements in caries prevention. If the health care provider has concerns regarding compliance, it might be best to consider other sources of fluoride exposure for the patient, such as ensuring regular twice daily use of fluoride toothpaste.¹

While dietary fluoride supplements can be effective in reducing tooth decay, there are several factors that can impede their use and resulting therapeutic value:

- Patients/parents/caregivers must have access to a professional health care provider who can conduct the necessary assessments and provide prescriptions for dietary fluoride supplements repeatedly over time, often needing adjustment based on age and changes in water sources.
- The dietary fluoride supplements must be obtained through a pharmacy/pharmaceutical service and refilled as necessary.
- The cost of the dietary fluoride supplements can be a financial hardship for some individuals.
- The compliance required (a child should take the supplement every day until 16 years of age) to obtain the optimal therapeutic effect often is difficult to achieve.
- Tablets and lozenges are manufactured with 1.0, 0.5, or 0.25 mg fluoride. To maximize the topical effect of fluoride, tablets and lozenges are intended to be chewed or sucked for 1–2 mins before being swallowed; for infants, supplements are available as a liquid and used with a dropper.

Noting the potential obstacles listed above, where feasible, community water fluoridation is preferred because it offers proven decay prevention benefits without the need for access to a health care professional or a change in behavior on the part of the individual. Simply by drinking water at home, school, work, or play, everyone in the community benefits regardless of socioeconomic status, educational attainment, or other social variables.⁶

While dietary fluoride supplements can reduce a child's risk of tooth decay, community water fluoridation extends that benefit to adults in the community. Additionally, the cost of dietary fluoride supplements over an extended period of time can be a financial concern to a family. In looking at overall costs, consideration should be given to the cost per person and the number of people who can benefit from a dietary fluoride supplement or community fluoridation program.⁷

¹ Rozier RG, Adair S, Graham F, et al. Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention: a report of the American dental association council on scientific affairs. *J Am Dent Assoc.* 2010;141(12):1480–1489.

² National Institutes of Health: Office of Dietary Supplements. Fluoride: fact sheet for health professionals. Accessed March 21, 2025. <https://ods.od.nih.gov/factsheets/Fluoride-HealthProfessional/>

³ Chou R, Bougatsos C, Griffin J, et al. Screening, referral, behavioral counseling, and preventive interventions for oral health in children and adolescents ages 5 to 17 years: a systematic review for the US preventive services task force. Rockville (MD), USA: Agency for Healthcare Research and Quality; 2023.

⁴ American Dental Association. Chairside tool: dietary fluoride supplements: evidence-based clinical recommendations. 2010. Accessed March 20, 2025. https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/resources/research/ada_evidence-based_fluoride_supplement_chairside_guide.pdf.

⁵ American Dental Association. Oral health topic: caries risk assessment and management. Accessed March 20, 2025. <https://www.ada.org/resources/ada-library/oral-health-topics/caries-risk-assessment-and-management>.

⁶ Horowitz HS. The effectiveness of community water fluoridation in the United States. *J Public Health Dent.* 1996;56(5 Spec No):253–258.


⁷ Garcia AI. Caries incidence and costs of prevention programs. *J Public Health Dent.* 1989;49(5 Spec No):259–271.

ATTACHMENT B

FLUORIDE SUPPLEMENT PRESCRIBING TRENDS AMONG DENTISTS

Economic Outlook and Emerging Issues in Dentistry

*Insights from Data from Q2 2025:
Fluoride Supplement Prescriptions*

 Health Policy Institute

ADA American Dental Association*

Key Takeaways

Nearly 2 in 3 dentists prescribe fluoride supplements to their patients.

Among those who prescribe fluoride supplements to **child patients**:

- Those who see only child patients most often prescribe *high-concentration fluoride toothpaste* (71.1%) and almost two-thirds prescribe *fluoride tablets* (62.8%).
- Those who see both child and adult patients most often recommend *more frequent application of fluoride varnish* (72.8%). About half prescribe *high-concentration fluoride toothpaste* (52.3%) or *fluoride rinse* (51.9%).

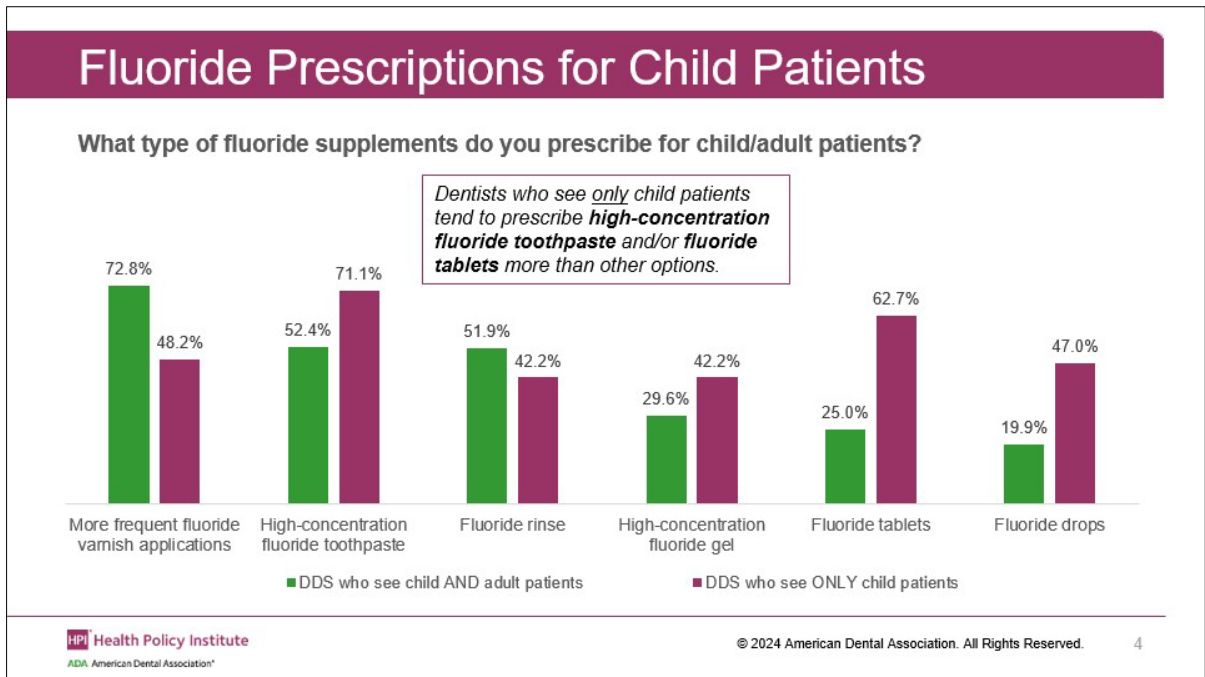
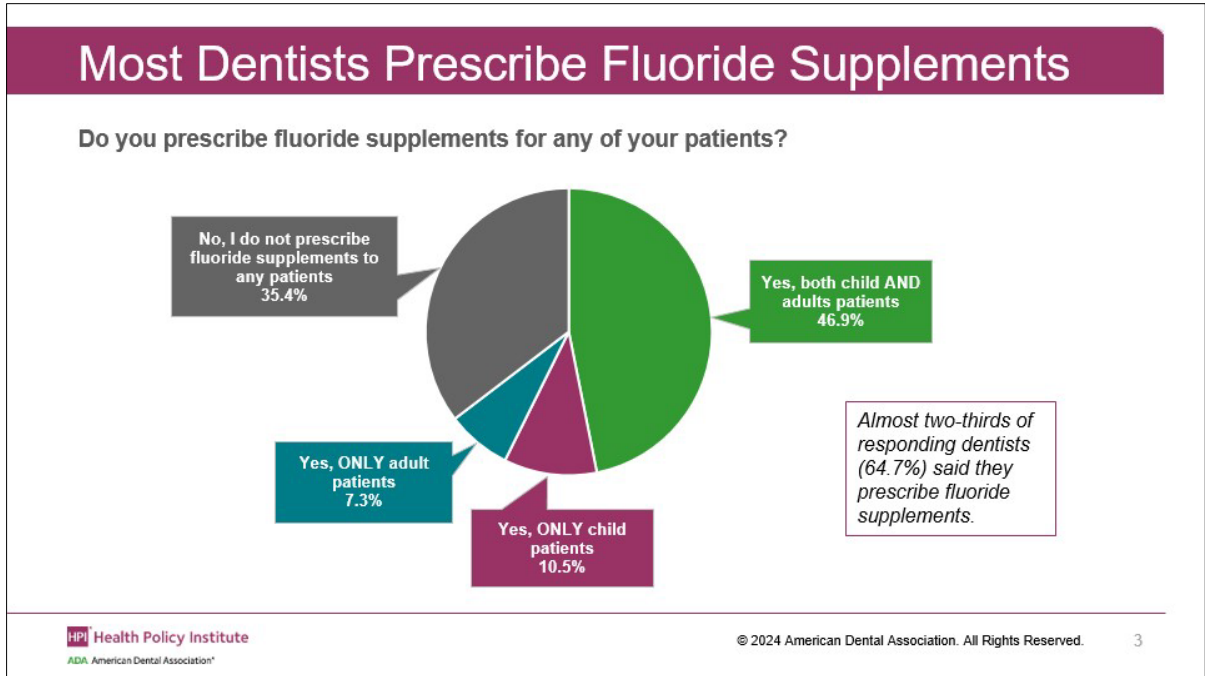
Among those who prescribe fluoride supplements to **adult patients**:

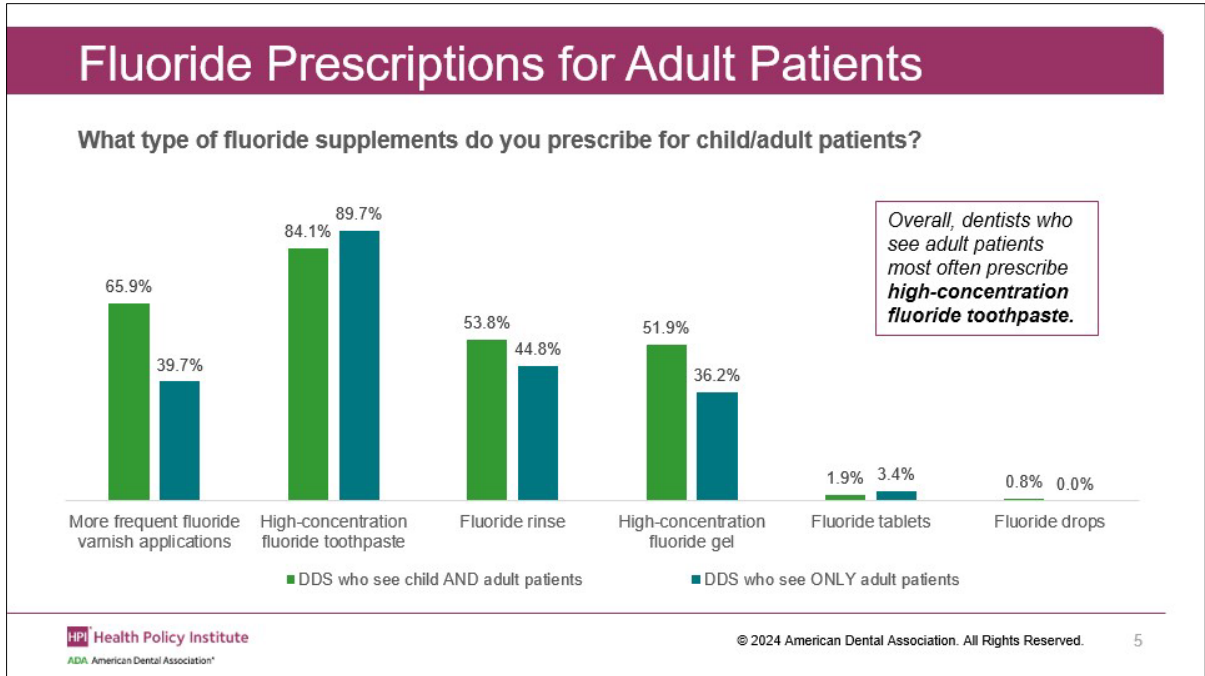
- Those who see both child and adult patients more often recommend *more frequent application of fluoride varnish* (65.9%), *fluoride rinse* (53.8%), or *high-concentration fluoride gel* (51.9%) compared to those who see only adult patients (39.7%, 44.8%, and 36.2%, respectively).
- Among all dentists who see adult patients, the most common type of fluoride supplement prescribed is *high-concentration fluoride toothpaste* (84.1% and 89.7%).

 Health Policy Institute
ADA American Dental Association*

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Methods

- These data were collected as part of a larger, quarterly, online poll originally launched in January 2022 with the goal to better understand the economic and operational conditions in dental practices and public health clinics over time and to measure the impact of emerging issues in dentistry.
- This quarter's poll was distributed to nearly 2,500 panel members; 799 dentists participated in Q2 2025.
- Data was collected June 16 - 22, 2025.
- Core measures: Economic confidence, patient wait times, busyness levels, recruitment needs and challenges, recent practice decisions.
- New in Q2 2025: **Dentists' prescription of fluoride supplements and types of fluoride supplements prescribed**, and actual and expected increases in practice expenses.
- Complete reports available at [ADA.org/HPI](https://ada.org/HPI).

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ATTACHMENT C

POTENTIAL HEALTH EFFECTS OF FLUORIDE ON NEURODEVELOPMENT AND COGNITION

The plurality of generally accepted scientific evidence does not support the hypothesis that fluoride ingestion has an adverse effect on IQ scores, certainly not at recommended levels of exposure.

Much has been made about a recent National Toxicology Program (NTP) monograph¹ and separately published meta-analysis² that purport to have uncovered an association between exposure to high levels of fluoride (≥ 1.5 mg/L) and IQ scores.³

While the report states there may be an association, the NTP website clarifies, “An association indicates a connection between fluoride and lower IQ; it does not prove a cause and effect.” The website further observes that “many substances are healthy and beneficial when taken in small doses,” as is the case with community water fluoridation (0.7 mg/L).⁴

The ADA therefore urges the Food and Drug Administration (FDA) to consider the following before giving weight to these documents.^{5,6,7,8,9} (Note that we have included some mentions of the Environmental Protection Agency (EPA), based on the agency’s press release of April 7, 2025, stating its intent to “expeditiously review new scientific information on potential health risks of fluoride in drinking water.”)

- NTP’s monograph and meta-analysis are based on 19 studies[†] conducted in six countries in areas where the fluoride content in drinking water is **far higher than what is typically found** in the United States—and more than double (≥ 1.5 mg/L) what the U.S. Public Health Service recommends for community water fluoridation (0.7 mg/L).
- The authors relied on studies that **did not adjust for confounders**—such as exposure to pollutants and naturally occurring minerals, radionuclides, heavy metals, and other substances. These substances can include selenium, uranium, arsenic, cadmium, and iron, as well as naturally occurring bacteria, viruses, and parasites.¹⁰
- The authors gave preference to studies that **relied on invalid biomarkers** to measure fluoride exposures, such as maternal spot urine analysis.¹¹
- The authors gave preference to studies that **used an unauthenticated survey instrument** to which outside observers have been repeatedly denied access.^{12,13} These proprietary data—from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study—are owned by CHU Sainte-Justine in Canada. The ADA would welcome assistance in accessing the raw data to validate the authors’ scientific analysis of it.
- The authors **weighted studies inconsistently**. For example, the original peer reviewer—the National Academies of Sciences, Engineering and Medicine (NASEM)—was twice unable to understand NTP’s methodology for favoring some study elements supporting its hypothesis while ignoring other elements from the same studies that refuted it.^{5,6,7,8,9} NASEM is considered the gold standard for peer review.
- The NTP **switched peer reviewers** after the original peer reviewer, NASEM, found the initial drafts would not survive scientific scrutiny.⁵ Changing peer reviewers is highly unorthodox, as is

[†] Of the seventy-two studies initially reviewed, almost three-fourths were judged, even by the authors, to be of low quality with a high risk for bias. Almost all were from areas in countries such as China, India, and Iran with very high levels of fluoride in their groundwater, as well as unknown contaminants from pollution and other sources.

replacing the original peer review panel with one of your own choosing. Again, NASEM is considered the gold standard for peer review.

- The NTP **used less stringent evaluation methods** than the Integrated Risk Information System (IRIS) program and Six-Year Review risk assessment methods the EPA is required to use to grade the biases, strengths, and weaknesses of existing studies.^{14, 15, 16, 17}

Importantly, the NTP monograph and separately published meta-analysis found no significant association between exposure to fluoride at the levels used in community water fluoridation (0.7 mg/L) and children's IQ scores.

Some noted researchers have called for a “blanket retraction” of the NTP monograph and separately published meta-analysis, comparing them to Andrew Wakefield’s 1998 paper in *The Lancet*, which was later retracted, insinuating a link between the measles-mumps-rubella vaccine and autism.^{9, 18} The paper, which was widely publicized, led to a decline in vaccination rates in the United States, the United Kingdom, and Ireland, and a corresponding rise in measles and mumps infections, resulting in serious illness and deaths.¹⁹

The ADA therefore urges FDA to consider the following before giving weight to the NTP report and separately published meta-analysis.

- **Table C-1** identifies studies that are likely **suitable** for an EPA IRIS review or Six-Year Review, based on the risk evaluation protocols established in the Safe Drinking Water Act.
- **Table C-2** identifies **critical** meta-analyses, evidence reviews, peer reviews, and commentaries. (Especially important is the literature examining the validity of using spot maternal urinary fluoride as a biomarker for studying effects of fluoride on the developing brain.)
- **Table C-3** identifies studies that are likely **not suitable** for an EPA IRIS review or Six-Year Review, based on the risk evaluation protocols established in the Safe Drinking Water Act.
- **Table C-4** identifies **questionable** meta-analyses, evidence reviews, and peer reviews, along with explanations of why.

Note that EPA last examined the safety of fluoride as part of its Six-Year Review 4 of Primary Drinking Water Standards, the results of which were published in July 2024.²⁰ EPA’s scientific reviewers determined the state of the literature did not justify a revision to the primary maximum contaminant level.

TABLE C-1. STUDIES THAT ARE LIKELY SUITABLE FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)	
<i>Study</i>	<i>Type</i>
Aggeborn L, Öhman M (2021) The effects of fluoride in drinking water. <i>J Polit Econ.</i> 129(2):465–491. https://doi.org/10.1086/711915	Longitudinal Study
Broadbent JM, Thomson WM, Ramrakha S, et al. Community Water Fluoridation and Intelligence: Prospective Study in New Zealand. <i>Am J Public Health.</i> 2015 Jan;105(1):72-76. doi: 10.2105/AJPH.2013.301857	Longitudinal Study
Broadbent JM, Thomson WM, Moffitt TE, Poulton R. Broadbent et al. Respond. <i>Am J Public Health.</i> 2016 Feb;106(2):213-4. doi: 10.2105/AJPH.2015.303013 .	

TABLE C-1. STUDIES THAT ARE LIKELY SUITABLE FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)	
<i>Study</i>	<i>Type</i>
Dewey D, England-Mason G, Ntanda H, et al; APrON Study Team. Fluoride exposure during pregnancy from a community water supply is associated with executive function in preschool children: A prospective ecological cohort study. <i>Sci Total Environ.</i> 2023 Sep 15;891:164322. doi: 10.1016/j.scitotenv.2023.164322 .	Cohort Study
Do LG, Sawyer A, John SA, et al. Early Childhood Exposures to Fluorides and Cognitive Neurodevelopment: A Population-Based Longitudinal Study. <i>J Dent Res.</i> 2025 Mar;104(3):243-250. doi: 10.1177/00220345241299352	Cohort Study
Do LG, Spencer AJ, Sawyer A, et al. Early Childhood Exposures to Fluorides and Child Behavioral Development and Executive Function: A Population-Based Longitudinal Study. <i>J Dent Res.</i> 2023 Jan;102(1):28-36. doi: 10.1177/00220345221119431 .	Cohort Study
Grandjean P, Meddis A, Nielsen F, Beck IH, et al. 2023. Dose dependence of prenatal fluoride exposure associations with cognitive performance at school age in three prospective studies. <i>Eur J Public Health</i> 34(1):143-419.	Risk Assessment Analysis
Ibarluzea J, Gallastegi M, Santa-Marina L, et al. Prenatal exposure to fluoride and neuropsychological development in early childhood: 1-to 4 years old children. <i>Environ Res.</i> 2022 May 1;207:112181. doi: 10.1016/j.envres.2021.112181 .	Cohort Study
Ibarluzea J, Subiza-Pérez M, Arregi A, et al. Association of maternal prenatal urinary fluoride levels with ADHD symptoms in childhood. <i>Environ Res.</i> 2023 Oct 15;235:116705. doi: 10.1016/j.envres.2023.116705 .	Cohort Study
Lin YY, Hsu WY, Yen CE, Hu SW. Association of Dental Fluorosis and Urinary Fluoride with Intelligence among Schoolchildren. <i>Children.</i> 2023 May 31;10(6):987. doi: 10.3390/children10060987 .	Cross-Sectional Study

TABLE C-2. CRITICAL ANALYSES	
<i>Publication</i>	<i>Type</i>
Canadian Agency for Drugs and Technologies in Health. Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects [Internet]. (CADTH rapid response report: summary with critical appraisal). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Oct 23. PMID: 31873994. https://www.ncbi.nlm.nih.gov/books/NBK551870/	Evidence Review
Canadian Agency for Drugs and Technologies in Health. Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects – A 2020 Update [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Nov 4. PMID: 33600099. https://www.ncbi.nlm.nih.gov/books/NBK567579/	

TABLE C-2. CRITICAL ANALYSES	
Publication	Type
Duan Q, Jiao J, Chen X, Wang X. Association between water fluoride and the level of children's intelligence: a dose-response meta-analysis. <i>Public Health</i> . 2018 Jan;154:87-97. doi: 10.1016/j.puhe.2017.08.013 .	Meta-Analysis
Farmus L, Till C, Green R, et al. ADDENDUM: Critical windows of fluoride neurotoxicity in Canadian Children. <i>Environ Res</i> . 2022 Dec;215(Pt. 3):114468. doi: 10.1016/j.envres.2022.114468 . Erratum for: <i>Environ Res</i> . 2021 Sep;200:111315. doi: 10.1016/j.envres.2021.111315 .	Erratum
Fiore G, Veneri F, Di Lorenzo R, et al. Fluoride Exposure and ADHD: A Systematic Review of Epidemiological Studies. <i>Medicina (Kaunas)</i> . 2023 Apr 19;59(4):797. doi: 10.3390/medicina59040797 .	Evidence Review
Guichon JR, Cooper C, Rugg-Gunn A, Dickinson JA. Flawed MIREC fluoride and intelligence quotient publications: A failed attempt to undermine community water fluoridation. <i>Community Dent Oral Epidemiol</i> . 2024 Aug;52(4):365-374. doi: 10.1111/cdoe.12954 .	Analysis
Guth S, Hüser S, Roth A, et al. Contribution to the ongoing discussion on fluoride toxicity. <i>Arch Toxicol</i> . 2021 Jul;95(7):2571-2587. doi: 10.1007/s00204-021-03072-6 .	Evidence Review
Guth S, Hüser S, Roth A, et al. Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses. <i>Arch Toxicol</i> . 2020 May;94(5):1375-1415. doi: 10.1007/s00204-020-02725-2 .	Evidence Review
Health Canada. Expert Panel Meeting on the Health Effects of Fluoride in Drinking Water: Summary report, January 2024. ISBN: 978-0-660-69864-9. Available at https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/expert-panel-meeting-effects-fluoride-drinking-summary.html (Accessed May 23, 2025)	Evidence Review
Jané MB, Heathers J, Grimes DR. 2025. Major Flaws in Taylor Et Al.'s (2025) Meta-analysis on Fluoride Exposure and Children's IQ Scores. <i>OSF Preprints</i> . March 10. doi: 10.31219/osf.io/zhm54_v3 .	Analysis
Jack B, Ayson M, Lewis S, et al. 2016. Health Effects of Water Fluoridation: Evidence Evaluation Report, report to the National Health and Medical Research Council, Canberra. Available at https://www.nhmrc.gov.au/about-us/publications/water-fluoridation-dental-and-other-human-health-outcomes (Accessed May 20, 2025)	Evidence Review
Kumar JV, Moss ME, Liu H, Fisher-Owens S. Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation. <i>Public Health</i> . 2023 Jun;219:73-84. doi: 10.1016/j.puhe.2023.03.011 .	Meta-Analysis

TABLE C-2. CRITICAL ANALYSES	
<i>Publication</i>	<i>Type</i>
Lambe K, Farragher A, Moloney T, et al. Impact of community water fluoridation on systemic health excluding oral health: An evidence review. Dublin: Health Research Board; 2022. Available at https://www.hrb.ie/publications (Accessed May 20, 2025)	Evidence Review
Levy SM. Caution needed in interpreting the evidence base on fluoride and IQ. <i>JAMA Pediatr.</i> 2025;179(3):231-234. doi: 10.1001/jamapediatrics.2024.5539	Commentary
Miranda GHN, Alvarenga MOP, Ferreira MKM, et al. A systematic review and meta-analysis of the association between fluoride exposure and neurological disorders. <i>Sci Rep.</i> 2021 Nov 22;11(1):22659. doi: 10.1038/s41598-021-99688-w .	Meta-Analysis
Moore D, Glenny AM. Fluoride and children's IQ: evidence of causation lacking. <i>Evid Based Dent.</i> 2024 Jun;25(2):95-97. doi: 10.1038/s41432-024-01022-6 .	Analysis
National Academies of Sciences Engineering and Medicine. Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report. Washington, DC: The National Academies Press 2021. https://doi.org/10.17226/26030	Peer Review
New Zealand Ministry of Health. 2024. Community Water Fluoridation: An evidence review. Wellington: Ministry of Health. Available at https://www.health.govt.nz/publications/community-water-fluoridation-an-evidence-review (Accessed May 20, 2025)	Evidence Review
Veneri F, Vinceti M, Generali L, et al. Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. <i>Environ Res.</i> 2023 Mar 15;221:115239. doi: 10.1016/j.envres.2023.115239 .	Meta-Analysis
<i>Urinary Fluoride as a Biomarker of Exposure</i>	
Aylward LL, Hays SM, Vezina A, et al. Biomonitoring Equivalents for interpretation of urinary fluoride. <i>Regul Toxicol Pharmacol.</i> 2015 Jun;72(1):158-67. doi: 10.1016/j.yrtph.2015.04.005 .	Analysis
Thomas DB, Basu N, Martinez-Mier EA, et al. Urinary and plasma fluoride levels in pregnant women from Mexico City. <i>Environ Res.</i> 2016 Oct;150:489-495. doi: 10.1016/j.envres.2016.06.046 .	Analysis
Villa A, Anabalon M, Zohouri V, et al. Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. <i>Caries Res.</i> 2010;44(1):60-8. doi: 10.1159/000279325 .	Analysis

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Bashash M, Thomas D, Hu H, et al. Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 Years of Age in Mexico. <i>Environ Health Perspect.</i> 2017 Sep 19;125(9):097017. doi: 10.1289/EHP655 .	Longitudinal Study	<p>Multiple meta-analyses found a definitely high risk of bias for confounding, convenience sampling, and cluster sampling. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Authors exhibited selection bias in using only two of four systematically different cohorts, with loss to follow-up of more than 79 percent and 72 percent of participants for the IQ and GCI analysis, respectively.</p> <p>Authors used on an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)</p> <p>Study was not compliant with the STROBE research methodology, which is a best practice for studies of this kind.</p> <p>Authors acknowledged they could not rule out confounders, such as unhealthy diets (i.e., salt intake).</p> <p>Authors acknowledged their null hypothesis was not proven.</p>
Choi AL, Zhang Y, Sun G, et al. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study. <i>Neurotoxicol Teratol.</i> 2015 Jan-Feb;47:96-101. doi: 10.1016/j.ntt.2014.11.001 .	Cross-Sectional Study	<p>Sample size was too small (i.e., 51 children).</p> <p>Study examines unrelated exposure variables (e.g., dental fluorosis is a postnatal phenomenon).</p> <p>Authors did not publish the results of the main study.</p>

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Cui Y, Yu J, Zhang B, et al. The relationships between thyroid-stimulating hormone and/or dopamine levels in peripheral blood and IQ in children with different urinary iodine concentrations. <i>Neurosci Lett.</i> 2020 Jun 11;729:134981. doi: 10.1016/j.neulet.2020.134981 .	Cross-Sectional Study	Overlapping publication from Tianjin City by Yu et al., 2018. Study was designed to evaluate dopamine levels, not associations between urinary fluoride and IQ scores. Multiple meta-analyses found a definitely high risk of bias for having a complex cross-sectional study design, selection bias, and more. (See Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.) Study design is vulnerable to Type 1 errors (false positives). Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)
Cui Y, Zhang B, Ma J, et al. Dopamine receptor D2 gene polymorphism, urine fluoride, and intelligence impairment of children in China: A school-based cross-sectional study. <i>Ecotoxicol Environ Saf.</i> 2018 Dec 15;165:270-277. doi: 10.1016/j.ecoenv.2018.09.018 .	Cross-Sectional Study	Overlapping publication from the Tianjin study by Yu et al., 2018. Study was designed to examine gene polymorphism, not associations between urinary fluoride and IQ scores. Multiple meta-analyses found a definitely high risk of bias for having a complex cross-sectional study design, selection bias, and more. (See Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.) Complex study design underestimates standard errors and is vulnerable to a Type 1 error (false positive). Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Ding Y, YanhuiGao, Sun H, et al. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. <i>J Hazard Mater.</i> 2011 Feb 28;186(2-3):1942-6. doi: 10.1016/j.jhazmat.2010.12.097 .	Cross-Sectional Study	Multiple meta-analyses found probably high risk of bias. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.) Authors did not adequately explain age-adjusted regression coefficient. Authors failed to adjust for confounders (e.g., socioeconomic factors, parental education, etc.).
Farmus L, Till C, Green R, et al. Critical windows of fluoride neurotoxicity in Canadian children. <i>Environ Res.</i> 2021 Sep;200:111315. doi: 10.1016/j.envres.2021.111315 . Erratum in: <i>Environ Res.</i> 2022 Dec;215(Pt. 3):114468. doi: 10.1016/j.envres.2022.114468.	Longitudinal Study	Farmus L, Till C, Green R, et al. ADDENDUM: Critical windows of fluoride neurotoxicity in Canadian Children. <i>Environ Res.</i> 2022 Dec;215(Pt. 3):114468. doi: 10.1016/j.envres.2022.114468 . Erratum for: <i>Environ Res.</i> 2021 Sep;200:111315. doi: 10.1016/j.envres.2021.111315.

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Green R, Lanphear B, Hornung R, et al. Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. <i>JAMA Pediatr.</i> 2019 Oct 1;173(10):940-948. doi: 10.1001/jamapediatrics.2019.1729 .	Longitudinal Study	<p>Multiple meta-analyses found high risk of bias for confounding, selection bias, and invalid biomarkers. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Authors used an unauthenticated survey instrument. (See Guichon 2024, in ATTACHMENT B.)</p> <p>Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)</p> <p>Study design exhibited selection bias (e.g., participants were matched within city).</p> <p>Study did not adjust for confounders (e.g., maternal IQ scores).</p> <p>Authors did not report the overall association between fluoride and child IQ scores.</p>
Rocha-Amador D, Navarro ME, Carrizales L, et al. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. <i>Cad Saude Publica.</i> 2007;23 Suppl 4:S579-87. doi: 10.1590/s0102-311x2007001600018 .	Cross-Sectional Study	<p>Multiple meta-analyses found probably high risk of bias for selective reporting. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Indirect evidence of selective reporting (i.e., presence of arsenic was noted but not factored into the results).</p>
Saxena S, Sahay A, Goel P. Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. <i>J Neurosci Rural Pract.</i> 2012 May;3(2):144-9. doi: 10.4103/0976-3147.98213 .	Cross-Sectional Study	<p>Authors acknowledged biased results due to inappropriate statistical analysis (i.e., no adjustment for area-level clustering in multivariate analyses).</p>

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Seraj B, Shahrabi M, Shadfar M, et al. Effect of high water fluoride concentration on the intellectual development of children in makoo/iran. <i>J Dent</i> (Tehran). 2012 Summer;9(3):221-9. PMID: 23119131; PMCID: PMC3484826 .	Cross-Sectional Study	Multiple meta-analyses found probably high risk of bias for clustering. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)
Soto-Barreras U, Escalante-Villalobos KY, Holguin-Loya B, et al. Effect of fluoride in drinking water on dental caries and IQ in children. <i>Fluoride</i> . 2019;52:474-482.	Cross-Sectional Study	Multiple meta-analyses rated the study as having a high risk of bias for confounding. (See Duan 2018, Kumar 2023, Veneri 2023, in ATTACHMENT B.)
Sudhir KM, Chandu GN, Prashant GM, Subba Reddy VV. Effect of fluoride exposure on intelligence quotient (IQ) among 13-15 year old school children of known endemic area of fluorosis, Nalgonda District, Andhra Pradesh. <i>J Indian Assoc Public Health Dent</i> . 2009(13):89-92.	Cross-Sectional Study	Multiple meta-analyses found probably high risk of bias for inadequate blinding. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)
Till C, Green R, Flora D, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. <i>Environ Int</i> . 2020 Jan;134:105315. doi: 10.1016/j.envint.2019.105315	Longitudinal Study	Moore D, Glenn AM. Fluoride and children's IQ: evidence of causation lacking. <i>Evid Based Dent</i> . 2024 Jun;25(2):95-97. doi: 10.1038/s41432-024-01022-6 .
Trivedi M, Sangai N, Patel R, et al. Assessment of groundwater quality with special reference to fluoride and its impact on IQ of schoolchildren in six villages of the Mundra Region, Kachchh, Gujarat, India. <i>Fluoride</i> . 2012;45(4):377-383.	Cross-Sectional Study	Multiple meta-analyses rated the study as having a probably high risk of bias for clustering. (See Duan 2018, Kumar 2023, Veneri 2023, in ATTACHMENT B.) Sampling methods do not account for population similarity. Recruitment methods, participation rates, and exclusion criteria were not provided. Blinding and other methods to reduce bias were not reported.

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Wang G, Gao M, Zhang M, et al. Correlation between total fluoride intake and children's IQ. <i>J Southeast Univ Med Ed.</i> 2012;743-746.	Cross-Sectional Study	Overlapping publication with Xiang 2003. Multiple meta-analyses rated the study as having a probably high risk of bias for fluoride intake. (See Duan 2018, Kumar 2023, Veneri 2023, in ATTACHMENT B.)
Wang M, Liu L, Li H, et al. Thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-age children. <i>Environ Int.</i> 2020 Jan;134:105229. doi: 10.1016/j.envint.2019.105229 .	Cross-Sectional Study	Overlapping publication Yu et al., 2018, from Tianjin City. Study was designed to examine thyroid function, not associations between urinary fluoride and IQ scores. Multiple meta-analyses found a definitely high risk of bias for having a complex cross-sectional study design, selection bias, and more. (See Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.) Complex study design underestimates standard errors and is vulnerable to a Type 1 error (false positive). Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Xiang Q, Liang Y, Chen L, et al. Effect of fluoride in drinking water on children's intelligence. <i>Fluoride</i> . 2003;36:84-94.	Cross-Sectional Study	<p>Multiple meta-analyses found high risk of bias. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Authors presented tables with bivariate comparisons but without multivariable models.</p> <p>Authors acknowledged they could not rule out confounders, such as increasing age and family income. The authors noted, "[t]he reason why there was the tendency for IQ scores to decrease with increasing age is not clear," and "no relationship was found between IQ scores and family income."</p>
Yu X, Chen J, Li Y, et al. Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis and loss of excellent intelligence. <i>Environ Int</i> . 2018 Sep;118:116-124. doi: 10.1016/j.envint.2018.05.042 .	Cross-Sectional Study	<p>Largest fluoride-IQ score study (n=2886) conducted in Tianjin City.</p> <p>Multiple meta-analyses found a definitely high risk of bias for having a complex cross-sectional study design, selection bias, and more. (See Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Complex study design underestimates standard errors and is vulnerable to Type 1 errors (false positives).</p> <p>Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)</p>

TABLE C-3. STUDIES THAT ARE LIKELY <u>NOT SUITABLE</u> FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)		
<i>Unsuitable Study</i>	<i>Type</i>	<i>Context</i>
Zhang S, Zhang X, Liu H, et al. Modifying effect of COMT gene polymorphism and a predictive role for proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China. <i>Toxicol Sci.</i> 2015 Apr;144(2):238-45. doi: 10.1093/toxsci/kfu311 .	Cross-Sectional Study	<p>Overlapping publication with Yu et al., 2018, from Tianjin City.</p> <p>Study was designed to examine gene polymorphism, not associations between urinary fluoride and IQ scores.</p> <p>Multiple meta-analyses found a definitely high risk of bias for having a complex cross-sectional study design, selection bias, and more. (See Duan et al., 2018; Kumar et al., 2023; Miranda et al., 2021; Veneri et al., 2023; in ATTACHMENT B.)</p> <p>Complex study design underestimates standard errors and is vulnerable to a Type 1 error (false positive).</p> <p>Authors used an invalid biomarker (i.e., urinary fluoride samples). (See Aylward et al., 2015; Thomas et al., 2016; and Villa et al., 2010; in ATTACHMENT B.)</p>

TABLE C-4. QUESTIONABLE ANALYSES		
Questionable Analysis	Type	Context
<p>National Toxicology Program (NTP). 2024. NTP monograph on the state of the science concerning fluoride exposure and neurodevelopment and cognition: a systematic review. Research Triangle Park, NC: National Toxicology Program. NTP Monograph 08. https://doi.org/10.22427/NTP-MGRAPH-8</p>	<p>Monograph</p>	<p>National Academies of Sciences Engineering and Medicine. Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report. Washington, DC: The National Academies Press 2021. https://doi.org/10.17226/26030</p> <p>Jané MB, Heathers J, and Grimes DR. 2025. Major Flaws in Taylor et al.'s (2025) Meta-analysis on Fluoride Exposure and Children's IQ Scores. <i>OSF Preprints</i>. March 10. doi: 10.31219/osf.io/zhm54_v3.</p> <p>Levy SM. Caution needed in interpreting the evidence base on fluoride and IQ. <i>JAMA Pediatr</i>. 2025;179(3):231-234. doi: 10.1001/jamapediatrics.2024.5539</p> <p>* Additional critiques of this monograph are available.</p>
<p>Taher MK, Momoli F, Go J, et al. Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water. <i>Crit Rev Toxicol</i>. 2024 Jan;54(1):2-34. doi: 10.1080/10408444.2023.2295338.</p>	<p>Evidence Review</p>	<p>Less weight should be given to the ecological and cross-sectional studies relative to the few prospective cohort studies of individuals exposed to fluoride levels in the range of concern with longitudinal measurements of neurocognitive function. (See Health Canada, 2024, in ATTACHMENT A.)</p>

TABLE C-4. QUESTIONABLE ANALYSES		
Questionable Analysis	Type	Context
<p>Taylor KW, Eftim SE, Sibrizzi CA, et al. Fluoride Exposure and Children’s IQ Scores: A Systematic Review and Meta-Analysis. <i>JAMA Pediatr.</i> 2025;179(3):282–292. doi:10.1001/jamapediatrics.2024.5542</p>	<p>Meta-Analysis</p>	<p>National Academies of Sciences Engineering and Medicine. Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report. Washington, DC: The National Academies Press 2021. https://doi.org/10.17226/26030</p> <p>Jané MB, Heathers J, and Grimes DR. 2025. Major Flaws in Taylor et al.’s (2025) Meta-analysis on Fluoride Exposure and Children’s IQ Scores. <i>OSF Preprints</i>. March 10. doi:10.31219/osf.io/zhm54_v3.</p> <p>Levy SM. Caution needed in interpreting the evidence base on fluoride and IQ. <i>JAMA Pediatr.</i> 2025;179(3):231-234. doi:10.1001/jamapediatrics.2024.5539</p> <p>* Additional critiques of this meta-analysis are available, including ATTACHMENT A.</p>

¹ National Toxicology Program (NTP). 2024. NTP monograph on the state of the science concerning fluoride exposure and neurodevelopment, and cognition: a systematic review. Research Triangle Park, NC: National Toxicology Program. NTP Monograph 08. <https://doi.org/10.22427/NTP-MGRAPH-8>

² Taylor KW, Eftim SE, Sibrizzi CA, et al. Fluoride Exposure and Children’s IQ Scores: A Systematic Review and Meta-Analysis. *JAMA Pediatr.* 2025;179(3):282–292. doi:10.1001/jamapediatrics.2024.5542

³ Environmental Protection Agency, “EPA Will Expediently Review New Science on Fluoride in Drinking Water,” news release, April 7, 2025, <https://www.epa.gov/newsreleases/epa-will-expeditiously-review-new-science-fluoride-drinking-water>.

⁴ National Institute for Environmental Health Sciences, National Toxicology Program. Fluoride Exposure: Neurodevelopment and Cognition. Available at <https://ntp.niehs.nih.gov/research/assessments/noncancer/completed/fluoride>. (Accessed May 30, 2025)

⁵ National Academies of Sciences, Engineering, and Medicine. 2021. Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Letter Report. Washington, DC: The National Academies Press. doi:10.17226/26030

⁶ American Dental Association (April 28, 2023). Letter from American Dental Association to the NTP Board of Scientific Counselors. [Unpublished letter.]

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- ⁷ American Dental Association, Statement on the NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review, Before the NTP Board of Scientific Counselors (May 4, 2023) (testimony of Howard Pollick on behalf of the American Dental Association).
- ⁸ Levy SM. Caution needed in interpreting the evidence base on fluoride and IQ. *JAMA Pediatr.* 2025;179(3):231-234. doi:10.1001/jamapediatrics.2024.5539
- ⁹ Jané MB, Heathers J, and Grimes DR. 2025. Major Flaws in Taylor Et Al.'s (2025) Meta-analysis on Fluoride Exposure and Children's IQ Scores. *OSF Preprints.* March 10. doi:10.31219/osf.io/zhm54_v3.
- ¹⁰ Karim BA, Mahmood G, Hasija M, Meena B, Sheikh S. Assessment of heavy metal contamination in groundwater and its implications for dental and public health. *Chemosphere.* 2024 Nov;367:143609. doi: 10.1016/j.chemosphere.2024.143609. Epub 2024 Nov 1. PMID: 39461441.
- ¹¹ Kumar JV, Moss ME, Liu H, Fisher-Owens S. Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation. *Public Health.* 2023;219: 73-84. doi.org/10.1016/j.puhe.2023.03.011
- ¹² CHU Sainte-Justine Research Centre (September 18, 2020). Letter from Nicole Lupien, MIREC Biobank Manager, to Mark Moss, Associate Professor, ECU School of Dental Medicine. [Unpublished letter.]
- ¹³ CHU Sainte-Justine Research Centre (March 15, 2021). Letter from William Fraser, Chair, MIREC Biobank Management Committee, to Mark Moss, Associate Professor, ECU School of Dental Medicine. [Unpublished letter.]
- ¹⁴ National Toxicology Program, Office of Health Assessment and Translation. 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC. Available at <https://ntp.niehs.nih.gov/go/ohathandbook>. (Accessed May 21, 2025)
- ¹⁵ Environmental Protection Agency. ORD Staff Handbook for Developing IRIS Assessments (2022). EPA Office of Research and Development, Washington, DC, EPA/600/R-22/268, 2022.
- ¹⁶ 42 U.S. Code § 300g-1
- ¹⁷ Environmental Protection Agency, Six-Year Review of Drinking Water Standards. Available at <https://www.epa.gov/dwsixyearreview>. (Accessed May 27, 2025)
- ¹⁸ Editors of *The Lancet*, "Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children," *Lancet* 375, no. 9713 (February 2010): 445.
- ¹⁹ Rao TS, Andrade C. The MMR vaccine and autism: Sensation, refutation, retraction, and fraud. *Indian J Psychiatry.* 2011 Apr;53(2):95-6. doi: 10.4103/0019-5545.82529. PMID: 21772639; PMCID: PMC3136032.
- ²⁰ Environmental Protection Agency. "National Primary Drinking Water Regulations; Announcement of the Results of EPA's Fourth Review of Existing Drinking Water Standards." Federal Register 89, no. 141 (July 23, 2024): 59623. Available at <https://www.federalregister.gov/documents/2024/07/23/2024-15807/national-primary-drinking-water-regulations-announcement-of-the-results-of-epas-fourth-review-of>. (Accessed May 27, 2025)

ATTACHMENT D

POTENTIAL HEALTH EFFECTS OF FLUORIDE ON THE GUT MICROBIOME

The plurality of generally accepted scientific evidence does not support the hypothesis that fluoride ingestion has an adverse effect on the gut microbiome, certainly not at recommended levels of exposure.

Most of the peer-reviewed publications on the topic are animal studies, and those studies have had mixed results that cannot be extrapolated to human beings. In fact, one systematic review identified in FDA's May 13 press release for this meeting concluded that "none of the studies retrieved examined the effects of ingested fluoridated water on the human microbiome."¹

Another systematic review cited in that press release included a total of two human studies, both of which were conducted in endemic fluorosis regions of China.² One was a cross-sectional study that included 32 adults who had skeletal fluorosis for at least 10 years and whose fluoride exposure was from indoor burning of coal with exceptionally high fluoride content and 33 healthy controls.³ Skeletal fluorosis does not occur in the United States.

The other study included 9 children with dental fluorosis and 13 children without fluorosis.⁴ Both studies had major limitations in design, conduct, and reporting, both were conducted in regions with levels of fluoride exposure that have no relevance to the United States, and neither study can determine whether fluoride ingestion alters the gut microbiome.

Another study included in that systematic review was a Chinese *ex vivo* experimental study in which investigators examined the microbiome in fecal samples from four young, healthy volunteers.⁵ The researchers mixed fecal material with water with varying concentrations of fluoride (0, 1, 2, 10 and 15 mg fluoride per L) and measured changes in gut microbiome. They found no microbiome changes at 1 mg/L or 2 mg/L, the fluoride concentrations most relevant to exposure levels in the United States from fluoridated water or fluoride supplements.

The ADA would welcome additional research on this topic. But for now, the question of whether the human microbiome is altered by fluoride ingestion is just a hypothesis in search of a plurality of generally accepted evidence.

¹ Moran GP, Zgaga L, Daly B, Harding M, Montgomery T. Does fluoride exposure impact on the human microbiome? *Toxicol Lett.* 2023 Apr 15;379:11-19. doi: 10.1016/j.toxlet.2023.03.001. Epub 2023 Mar 4. PMID: 36871794.

² Yasin M, Zohoori FV, Kumah EA, Subramanian M, Dean P, Orr CH. Effect of Fluoride on Gut Microbiota: A Systematic Review. *Nutr Rev.* 2025 Jul 1;83(7):e1853-e1880. doi: 10.1093/nutrit/nuae202. PMID: 40063073; PMCID: PMC12166178.

³ Wang J, Yu C, Zhang J, Liu R, Xiao J. Aberrant gut microbiota and fecal metabolites in patients with coal-burning endemic fluorosis in Guizhou, China. *Environ Sci Pollut Res Int.* 2023 Jun;30(27):69913-69926. doi: 10.1007/s11356-023-27051-9. Epub 2023 May 4. PMID: 37140865.

⁴ Zhou G, Li Q, Hou X, Wu H, Fu X, Wang G, Ma J, Cheng X, Yang Y, Chen R, Li Z, Yu F, Zhu J, Ba Y. Integrated 16S rDNA sequencing and metabolomics to explore the intestinal changes in children and rats with dental fluorosis. *Ecotoxicol Environ Saf.* 2023 Feb;251:114518. doi: 10.1016/j.ecoenv.2023.114518. Epub 2023 Jan 12. PMID: 36640576.

⁵ Chen G, Hu P, Xu Z, Peng C, Wang Y, Wan X, Cai H. The beneficial or detrimental fluoride to gut microbiota depends on its dosages. *Ecotoxicol Environ Saf.* 2021 Feb;209:111732. doi: 10.1016/j.ecoenv.2020.111732. Epub 2020 Dec 26. PMID: 33373928.

ATTACHMENT E

POTENTIAL HEALTH EFFECTS OF FLUORIDE ON THYROID FUNCTION

The plurality of generally accepted scientific evidence indicates that fluoride does not have an adverse effect on the thyroid gland or its function, certainly not at recommended levels of exposure.

Several systematic reviews and individual studies completed in the last 15 years have looked at a possible association between exposure to fluoride and thyroid function. Much of the literature that reports an association is focused on excessive fluoride exposure^{1,2,3} at levels well above those currently recommended by the ADA and most public health institutions, and thus should not be used as evidence against fluoride exposure at recommended levels.

National Toxicology Program Monograph (2024)

The NTP Monograph⁴ systematically reviewed human, animal, and mechanistic studies on the thyroid gland and hormones on the extent and quality of the evidence linking fluoride exposure to neurodevelopmental and cognitive effects in humans (Question 41). Changes in thyroid hormones have been proposed as a potential mechanism for neurodevelopmental effects,^{5,6} which is why thyroid effects were also evaluated in the final report. The NTP report evaluated eight low risk-of-bias studies and 16 high risk-of-bias studies. The studies examined thyroid hormones—the thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4)—as markers of thyroid gland function. The evidence includes a mix of findings, with some variability across studies based on factors such as fluoride concentration, age, and study design. When examining associations between fluoride exposure and thyroid hormones (TSH, T3, and T4), studies that analyzed changes across all three hormones reported varied results, including increases, decreases, or no changes in hormone levels.

These studies also highlighted age-related differences in the associations between fluoride exposure and thyroid hormones. The findings indicate that while high levels of fluoride exposure may influence thyroid hormones, the evidence does not conclusively demonstrate that consuming fluoridated water at recommended levels adversely affects the thyroid gland or its function. The variability in study results and the complex interplay between the thyroid and other physiological systems suggest that any potential effects are not straightforward. Therefore, based on current evidence, fluoridated water at recommended concentrations is not clearly linked to negative impacts on thyroid health.⁴

Iamandii et al. (2023)

A 2023 systematic review³ of fluoride exposure and thyroid function evaluated data from studies conducted in Asia, Europe, Africa, and Canada. The authors examined low and high levels of naturally fluoridated water reported in the original papers. Thyroid function, as measured by TSH and T4, showed little or no impact related to water fluoride. It is important to note that community water fluoridation was not evaluated, and no US studies were included. Furthermore, results showed that levels of natural fluoride at the same level as that recommended in the United States (0.7 ppm) showed no negative impact on thyroid function or thyroid disease.³

Australian National Health and Medical Research Council Systematic Review (2017)

In 2017, the Australian National Health and Medical Research Council's systematic review Information Paper—Water Fluoridation: Dental and Other Human Health Outcomes⁷ concluded, "There is no reliable evidence of an association between water fluoridation and current Australian levels and thyroid function including goiter (enlargement of the thyroid gland) and hypothyroidism (underactive thyroid)." (Current recommendations for fluoride levels in drinking water in Australia are a range of 0.6–1.1 mg/L depending on climate.)⁷

USPHS Recommendation (2015)

In 2015, the *USPHS Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries*⁵ was released. It referred to the 2006 NRC's report, *Fluoride in Drinking Water—A Scientific Review of the EPA's Standards*,⁸ stating:

“The 2006 NRC review considered a potential association between fluoride exposure (2–4 mg/L) and changes in the thyroid, parathyroid, and pineal glands in experimental animals and humans.” The report noted that available studies of the effects of fluoride exposure on endocrine function have limitations. For example, many studies did not measure actual hormone concentrations, and several studies did not report nutritional status or other factors likely to confound findings. The NRC called for better measurement of exposure to fluoride in epidemiological studies and for additional research “to characterize the direct and indirect mechanisms of fluoride's action on the endocrine system and factors that determine the response, if any, in a given individual.”⁸

Scientific Committee on Health and Environmental Risks Report (2011)

A scientific evaluation of agents used in fluoridating drinking water was done by the Scientific Committee on Health and Environmental Risks (SCHER) as requested by the European Commission (EC).⁹ The EC is the European Union's (EU) executive body with responsibility to manage EU policy. The final report, *Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water*, was released in 2011. It stated, “A systematic evaluation of the human studies does not suggest a potential thyroid effect at realistic exposures to fluoride.”⁹

Highlighted Studies

The following studies provide additional evidence that consumption of optimally fluoridated water at levels recommended in the United States (0.7 mg/L) does not affect thyroid function:

- **Griebel-Thompson et al. (2023):** In 2023, a scoping review of maternal thyroid function and effects on offspring in relation to iodine and fluoride exposure during pregnancy was published.¹⁰

In this review, the authors stated that there were only two published studies^{11,12} on the effects of fluoride exposure in relation to iodide status that appropriately corrected for urinary concentration when measuring urinary iodine and fluoride concentrations. However, only the study on nonpregnant adults measured thyroid hormones.¹¹ The authors concluded that more studies are needed to inform our understanding of iodine intake and fluoride exposure in pregnant women.¹⁰
- Two studies have explored the association between fluoridated water and cancer of the thyroid gland.^{13,14} Both studies found no association between optimal levels of fluoride in drinking water and thyroid cancer.

¹ Chaitanya NCSK, Karunakar P, Allam NSJ, et al. A systematic analysis on possibility of water fluoridation causing hypothyroidism. *Indian J Dent Res.* 2018;29(3):358–363.

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ATTACHMENT F

OTHER HEALTH RISK CLAIMS

Since its inception over 80 years ago, some have raised questions about whether there is a causal relationship between fluoride exposure and all manner of ailments. Many studies touting evidence of harm have proven to be poorly designed, inconclusive, conflicting, misinterpreted, and widely mischaracterized.

In response, the ADA developed *Fluoridation Facts*. *Fluoridation Facts* is a compendium of answers to frequently asked questions about the safety, health benefits, and cost-effectiveness of not only community water fluoridation, but all fluoride exposures. Our goal is to provide clear, well-cited answers to help policy makers and the public navigate the many myths and misperceptions about this remarkably successful public health practice.

The 2025 edition of *Fluoridation Facts* debunks all manner of claims that fluoride is somehow associated with, among other things:

- Acquired immunodeficiency syndrome (AIDS)
- Allergic reactions (e.g., hair loss, contact burns)
- Accelerated aging
- Alzheimer's disease
- Arthritis
- Asthma
- Autism
- Behavioral problems (e.g., attention deficit disorders)
- Bone disease (e.g., osteoporosis, increased bone/hip fractures)
- Cancer (all types including osteosarcoma or bone cancer)
- Chronic bronchitis
- Colic (acute abdominal pain)
- Cystic fibrosis
- Down syndrome
- Emphysema
- Enzyme effects (gene alterations)
- Flatulence (gas)
- Gastrointestinal problems (irritable bowel syndrome)
- Harmful interactions with medications
- Heart disease
- Increased infant mortality
- Low birth weight for infants
- Kidney disease
- Lead poisoning
- Lethargy (lack of energy)
- Lower IQ scores
- Malpositioned teeth
- Parkinson's disease
- Pineal gland dysfunction (causing early puberty, chronic insomnia)
- Reproductive issues (damaged sperm, reduced fertility)
- Skin conditions (redness, rash/welts, itching)
- Sudden infant death syndrome (SIDS)

Fluoridation Facts also documents the symbiotic relationship between community water fluoridation and other fluoride sources, including community water fluoridation; fluoride-containing toothpastes and rinses; professionally applied fluoride foams, gels, and varnish; and prescription-strength supplements. These products work in concert with each other to prevent oral disease and improve oral health in a safe, comprehensive, and time-tested manner.

The 2025 edition of *Fluoridation Facts* is available now at www.ADA.org/fluoride. Please contact us if you have difficulty accessing the information you need.