AADOCR
American Association for Dental, Oral, and Craniofacial Research

February 27, 2026

Lee Zeldin, JD
Administrator,
Environmental Protection Agency,
1200 Pennsylvania Avenue, N.W.
Washington, DC, 20460

Re: Request for Comments on the Fluoride Preliminary Assessment Plan and Literature Survey.

via website: https://www.regulations.gov/docket/EPA-HQ-OW-2025-3823/document

The American Association for Dental, Oral, and Craniofacial Research (AADOCR) is the leading professional community for multidisciplinary scientists who advance dental, oral, and craniofacial research. We appreciate the opportunity to provide comments on EPA's Preliminary Assessment Plan and Literature Survey for the upcoming Fluoride Human Health Toxicity Assessment. To respond to this request for comments, AADOCR engaged its Science Information Committee.

We support the EPA's stated intent to use systematic review methods and to provide transparency early in the process, however, we urge EPA to strengthen the Assessment Plan to ensure the ultimate toxicity assessment is policy-relevant to U.S. drinking water exposures, methodologically coherent, and consistent with the principles the EPA invokes as "Gold Standard Science." Furthermore, we urge the EPA to seek an independent peer review of its assessment plan and systematic review by the National Academies of Sciences, Engineering, and Medicine (NASEM). This will assist in ensuring future regulatory decisions relative to community water fluoridation are based on reproducible, objective, and high-quality evidence.

1. Publish the full Systematic Review Protocol for public comment before proceeding

The plan outlines that it will develop a Systematic Review Protocol that will describe in detail study evaluation, identification of sensitive health effects, selection of best-suited studies for dose–response, and approaches to estimate total fluoride exposure (page 5-1). The AADOCR strongly recommends that EPA **publish the complete protocol for public comment prior to finalization and prior to completing the review**. This is critical as protocol-level decisions (comparability rules, exposure harmonization, risk-of-bias, effect-modifier handling, and analytic stratification) largely determine what evidence becomes most informative. Additionally, publishing the full protocol in advance will strengthen transparency, reproducibility, and stakeholder trust, and will help ensure that the final assessment is both scientifically defensible and clearly relevant to U.S. drinking water decision-making.

T +1.703.548.0066 | F +1.703.548.1883 | 1619 Duke Street, Alexandria, VA 22314-3406, USA | www.aadocr.org

Additionally, the assessment plan appropriately acknowledges that exposure biomarkers have material limitations (section 2.3), for example, that fluoride in blood or urine may be highly influenced by recent exposure rather than the typical / average exposure, and that different tissues/biomarkers reflect different time windows and pathways. It also notes that the criteria for evaluating exposure metrics and their ability to estimate etiologically relevant oral intake will be presented in the assessment protocol. As these exposure choices directly determine which studies can credibly support intake estimation and dose-response modeling, **AADOCR recommends EPA move key exposure-harmonization decisions forward and solicit public input on them as part of the protocol**, particularly rules for converting water concentration and biomarker measures into comparable intake estimates.

2. Update the literature search through 2025 and early 2026, and document search boundaries explicitly

The assessment plan relies on a very large body of evidence (i.e. 268,967 unique references) and automated tools to prioritize screening. Given the pace of publication in fluoride epidemiology, exposure science, and causal methods, timeliness becomes central to "gold standard" practice. Furthermore, an updated search window reduces the risk that conclusions are anchored to an incomplete or outdated evidence base, and it is especially important where small differences in study design, exposure measurement, and confounder control can materially affect hazard identification and dose-response modeling. Therefore, **AADOCR recommends that EPA** (i) **update the search to include 2025 through early 2026**, (ii) clearly document language limits, databases, and gray-literature policy, and (iii) rerun deduplication/prioritization with these updates so the protocol is built around the current evidence base.

3. Narrow and operationalize comparability: "any population" + "any exposure" is not a sufficient analytic frame

EPA's refined PECO (table 4.1) currently allows any population and lifestage and broadly includes any exposure to fluoride across oral/unknown/multiple routes during fetal-adolescent periods, with dental fluorosis and neurodevelopmental outcomes as priority endpoints. While broad searches can reduce selection bias, a search that spans multiple decades, heterogeneous geographies, and disparate measurement eras is not inherently unbiased unless EPA clearly specifies how it will harmonize evidence and avoid misleading equivalence across fundamentally non-comparable studies (Higgins et al., 2024). Older studies often used different analytical chemistry, exposure metrics, outcome instruments, and confounder control than contemporary studies. Treating all studies as equally informative, without explicit rules for comparability, risks conflating (i) measurement limitations of earlier eras with (ii) true health effects and can distort dose-response inference (Institute of Medicine of the National Academies, 2011, Edwards et al., 2017).

Therefore, **AADOCR recommends the protocol specifies explicit rules for comparability and a priori stratification**. This should include (at minimum):

i. exposure level bands relevant to U.S. drinking water contexts including explicit strata for exposure levels around 0.7 mg/L and ≤ 1.5 mg/L,
ii. exposure source context (naturally high fluoride vs managed community fluoridation, mixed sources),
iii. outcome ascertainment comparability (validated neurodevelopmental instruments, consistent fluorosis indices),
iv. core confounder sets and effect modifiers (nutrition, SES, co-exposures, altitude/renal factors, etc.), and
v. analytic handling of ecological vs individual exposure metrics.
vi. a clear framework for how the assessment will handle inconsistent evidence, null findings, and studies where data cannot be independently reviewed.

4. Guardrails for AI-enabled screening, clustering, and extraction must be explicit

EPA reports that AI and other automated tools were used to prioritize studies, followed by manual screening, and also describes supervised clustering and seed studies to prioritize dental dose-response candidates (section B.2.2.2.). AI-enabled screening and extraction can be efficient, but it also creates specific risks including (i). spurious correlations which can be amplified when heterogeneous observational studies are aggregated without tight causal assumptions and (ii). speculative narrative statements from discussion sections that may be elevated into “evidence” unless EPA uses strict extraction rules that distinguishes results from interpretation (Metelli et al., 2020, Irsova et al., 2025, Ge et al., 2024).

Therefore, **AADOCR recommends the**

i. full documentation of training/seed selection rationale,
ii. clear separation of association from causation throughout hazard identification and dose–response analyses,
iii. pre-specification of extraction rules that prioritize quantitative results (effect estimates, uncertainty measures) and explicitly exclude discussion-only speculation from being treated as evidentiary weight,
iv. a transparent QA/QC plan that (a) validates AI-assisted decisions against blinded human review samples at each stage and (b) reports how AI tools will be prevented from amplifying spurious correlations when aggregating heterogeneous observational studies.

5. Gold Standard Science requires targeted expertise and fit-for-purpose synthesis

Although systematic reviews can enhance transparency and reproducibility, gold standard is not achieved by scale alone. The plan has accurately noted that many studies lack sufficient data for dose-response and that others will be assessed for

suitability (section 4.2). Accordingly, we urge the EPA to avoid equating the quantity of papers included with better science and to ensure that a smaller set of well-designed studies are evaluated deeply by domain experts and are not diluted by a much larger set of weaker, less comparable studies.

AADOCR recommends that EPA pre-specify an evidence-ranking framework that prioritizes studies that are (a) methodologically robust, (b) exposure- and outcome-comparable with validated instruments, (c) appropriate confounder control and (d) policy-relevant exposure-level stratification (e.g., ≤0.7, 0.7–1.5, >1.5 mg/L) and context stratification (source of fluoride, co-exposures, nutrition). A large undifferentiated evidence pool can reduce clarity unless the protocol is designed to discern which studies are genuinely informative for dose–response derivation.

6. Clarify Fluorosis Adversity and Severity Thresholds Before Selecting the Critical Effect for RfD Derivation

The assessment plan describes dental fluorosis as a “well-established and sensitive” outcome and indicates a focus on identifying studies for RfD derivation. The plan acknowledges a "lack of consensus" on how to characterize the adversity of fluorosis but defers this critical decision. However, this choice is critical for determining which studies are selected for dose-response modeling, whether dental fluorosis or neurotoxicity becomes the critical effect, and ultimately the final reference dose (RfD) value. It is important to note that dental fluorosis is not a binary variable and must be assessed using an epidemiologic index (Dean’s Index, Thylstrup-Fejerskov Index, or the Horowitz Tooth Surface Index of Fluorosis). In the U.S., dental fluorosis is mostly mild and considered cosmetic not affecting tooth function (EPA, 2010 and US Centers for Disease Control and Prevention, 2024). As mild fluorosis has no deleterious or pathologic qualities, this makes it inappropriate for use as a threshold from which to determine toxicity. The EPA previously defined severe enamel fluorosis as the presence of enamel pitting (EPA, 2010). Combining all fluorosis severity levels conflates the distinction between cosmetic changes and clinically meaningful structural or functional impairment. Thereby, it leads to an inappropriately conservative toxicity value that does not reflect clinical reality. Therefore, **AADOCR urges the EPA to confine adverse outcomes for reference dose derivation to moderate-severe fluorosis.**

7. Ensure the final assessment includes interpretive guardrails to prevent misapplication

The EPA notes that the toxicity assessment will not be a full risk assessment and will not address policy considerations. The refined PECO also excludes studies of dental caries alone as primarily assessing beneficial effects. While that scoping choice is the EPA’s prerogative, **AADOCR urges EPA to include clear interpretive statements in the final toxicity document to reduce foreseeable misinterpretation**. This will

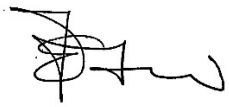
aid in reducing misapplication by clearly explaining that any derived value is a threshold for avoiding adverse effects, does not negate the well-documented caries-prevention benefits of fluoride at recommended levels.

AADOCR appreciates the EPA's commitment to a transparent process and the opportunity to provide comments in response to the *Fluoride Preliminary Assessment Plan and Literature Survey***.** AADOCR stands ready to work with the EPA and serve as a scientific resource as the EPA finalizes the protocol and proceeds to external peer review and public comment on the draft toxicity assessment.

If you have any further questions, please contact Dr. Makyba Charles-Ayinde, Director of Science Policy, at mcayinde@iadr.org.

Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer



Effie Ioannidou, DDS, MDS
President

References

Edwards JK, Keil AP. (2017). Measurement Error and Environmental Epidemiology: a Policy Perspective. *Curr Environ Health Rep*. 4(1):79-88.

Ge L, Agrawal R, Singer M, Kannapiran P, De Castro Molina JA, Teow KL, Yap CW, Abisheganaden JA. (2024). Leveraging artificial intelligence to enhance systematic reviews in health research: advanced tools and challenges. *Syst Rev*. 13(1):269.

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 (updated August 2024). Cochrane, 2024. Available from www.cochrane.org/handbook.

Institute of Medicine. *Finding What Works in Health Care: Standards for Systematic Reviews.* National Academies Press; 2011. Chapter 4 "Standards for Synthesizing the Body of Evidence."

Irsova, Z., Bom, P.R.D., Havranek, T. *et al.* (2025). Spurious precision in meta-analysis of observational research. *Nat Commun.* 16, 8454.

Metelli S, Chaimani A. (2020). Challenges in meta-analyses with observational studies. *Evid Based Ment Health*. 23(2):83-87.

US Centers for Disease Control and Prevention. (2024). About Dental Fluorosis. Retrieved from: https://www.cdc.gov/oral-health/about/about-dental-fluorosis.html. Accessed on February 24, 2026.

US Environmental Protection Agency (2010). EPA's Fluoride: Dose-Response Analysis for Non- Cancer Effects – Dental Fluorosis: Evaluations of Key Studies https://www.epa.gov/sites/default/files/2019-03/documents/fluoride-dose-response-noncancer-effects.pdf. Accessed February 24, 2026