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) monograph[1] and separately published meta-analysis[2] 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.)

Study	*Type*
Aggeborn L, Öhman M (2021) The effects of fluoride in drinking water. *J Polit Econ*. 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. *Am J Public Health*. 2015 Jan;105(1):72-76. doi: 10.2105/AJPH.2013.301857 Broadbent JM, Thomson WM, Moffitt TE, Poulton R. Broadbent et al. Respond. *Am J Public Health*. 2016 Feb;106(2):213-4. doi: 10.2105/AJPH.2015.303013.	Longitudinal Study

TABLE C-1. STUDIES THAT ARE LIKELY SUITABLE FOR A RIGOROUS REVIEW (Including those published since the NTP study period ended.)	
Study	*Type*
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. *Sci Total Environ*. 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. *J Dent Res*. 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. *J Dent Res*. 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. *Eur J Public Health* 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. *Environ Res*. 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. *Environ Res*. 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. *Children*. 2023 May 31;10(6):987. doi: 10.3390/children10060987.	Cross-Sectional Study

TABLE C-2. CRITICAL ANALYSES	
Publication	*Type*
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/ 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/	Evidence Review

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. *Public Health*. 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. *Environ Res*. 2022 Dec;215(Pt. 3):114468. doi: 10.1016/j.envres.2022.114468. Erratum for: *Environ Res*. 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. *Medicina (Kaunas)*. 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. *Community Dent Oral Epidemiol*. 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. *Arch Toxicol*. 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. *Arch Toxicol*. 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. *OSF Preprints*. 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. *Public Health*. 2023 Jun;219:73-84. doi: 10.1016/j.puhe.2023.03.011.	Meta-Analysis

TABLE C-2. CRITICAL ANALYSES	
Publication	*Type*
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. *JAMA Pediatr*. 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. *Sci Rep*. 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. *Evid Based Dent*. 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. *Environ Res*. 2023 Mar 15;221:115239. doi: 10.1016/j.envres.2023.115239.	Meta-Analysis
Urinary Fluoride as a Biomarker of Exposure	
Aylward LL, Hays SM, Vezina A, et al. Biomonitoring Equivalents for interpretation of urinary fluoride. *Regul Toxicol Pharmacol*. 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. *Environ Res*. 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. *Caries Res*. 2010;44(1):60-8. doi: 10.1159/000279325.	Analysis

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
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. *Environ Health Perspect*. 2017 Sep 19;125(9):097017. doi: 10.1289/EHP655.	Longitudinal Study	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.) 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. 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.) Study was not compliant with the STROBE research methodology, which is a best practice for studies of this kind. Authors acknowledged they could not rule out confounders, such as unhealthy diets (i.e., salt intake). Authors acknowledged their null hypothesis was not proven.
Choi AL, Zhang Y, Sun G, et al. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: a pilot study. *Neurotoxicol Teratol*. 2015 Jan-Feb;47:96-101. doi: 10.1016/j.ntt.2014.11.001.	Cross-Sectional Study	Sample size was too small (i.e., 51 children). Study examines unrelated exposure variables (e.g., dental fluorosis is a postnatal phenomenon). Authors did not publish the results of the main study.

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
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. *Neurosci Lett*. 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 associatons 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. *Ecotoxicol Environ Saf*. 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 NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
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. *J Hazard Mater*. 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. *Environ Res*. 2021 Sep;200:111315. doi: 10.1016/j.envres.2021.111315. Erratum in: *Environ Res*. 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. *Environ Res*. 2022 Dec;215(Pt. 3):114468. doi: 10.1016/j.envres.2022.114468. Erratum for: *Environ Res*. 2021 Sep;200:111315. doi: 10.1016/j.envres.2021.111315.

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
Green R, Lanphear B, Hornung R, et al. Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. *JAMA Pediatr*. 2019 Oct 1;173(10):940-948. doi: 10.1001/jamapediatrics.2019.1729.	Longitudinal Study	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.) Authors used an unauthenticated survey instrument. (See Guichon 2024, in ATTACHMENT B.) 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.) Study design exhibited selection bias (e.g., participants were matched within city). Study did not adjust for confounders (e.g., maternal IQ scores). Authors did not report the overall association between fluoride and child IQ scores.
Rocha-Amador D, Navarro ME, Carrizales L, et al. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. *Cad Saude Publica*. 2007;23 Suppl 4:S579-87. doi: 10.1590/s0102-311x2007001600018.	Cross-Sectional Study	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.) Indirect evidence of selective reporting (i.e., presence of arsenic was noted but not factored into the results).
Saxena S, Sahay A, Goel P. Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. *J Neurosci Rural Pract*. 2012 May;3(2):144-9. doi: 10.4103/0976-3147.98213.	Cross-Sectional Study	Authors acknowledged biased results due to inappropriate statistical analysis (i.e., no adjustment for area-level clustering in multivariate analyses).

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
Seraj B, Shahrabi M, Shadfar M, et al. Effect of high water fluoride concentration on the intellectual development of children in makoo/iran. *J Dent* (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. *Fluoride*. 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. *J Indian Assoc Public Health Dent*. 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. *Environ Int*. 2020 Jan;134:105315. doi: 10.1016/j.envint.2019.105315	Longitudinal Study	Moore D, Glenny AM. Fluoride and children's IQ: evidence of causation lacking. *Evid Based Dent*. 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, Gujurat, India. *Fluoride*. 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 NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
Wang G, Gao M, Zhang M, et al. Correlation between total fluoride intake and children's IQ. *J Southeast Univ Med Ed*. 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. *Environ Int*. 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 NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
Xiang Q, Liang Y, Chen L, et al. Effect of fluoride in drinking water on children's intelligence. *Fluoride*. 2003;36:84-94.	Cross-Sectional Study	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.) Authors presented tables with bivariate comparisons but without multivariable models. 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."
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. *Environ Int*. 2018 Sep;118:116-124. doi: 10.1016/j.envint.2018.05.042.	Cross-Sectional Study	Largest fluoride-IQ score study (n=2886) conducted in Tianjin City. 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 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.)

TABLE C-3. STUDIES THAT ARE LIKELY NOT SUITABLE FOR A RIGOROUS REVIEW
(Including those published since the NTP study period ended.)

Unsuitable Study	*Type*	*Context*
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. *Toxicol Sci*. 2015 Apr;144(2):238-45. doi: 10.1093/toxsci/kfu311.	Cross-Sectional Study	Overlapping publication with Yu et al., 2018, from Tianjin City. 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 Duan et al., 2018; 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-4. QUESTIONABLE ANALYSES		
Questionable Analysis	*Type*	*Context*
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	Monograph	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 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. 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 * Additional critiques of this monograph are available.
Taher MK, Momoli F, Go J, et al. Systematic review of epidemiological and toxicological evidence on health effects of fluoride in drinking water. *Crit Rev Toxicol*. 2024 Jan;54(1):2-34. doi: 10.1080/10408444.2023.2295338.	Evidence Review	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.)

TABLE C-4. QUESTIONABLE ANALYSES		
Questionable Analysis	*Type*	*Context*
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	Meta-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 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. 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 * Additional critiques of this meta-analysis are available, including ATTACHMENT A.

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