NTP Monograph
Fluoride Exposure and Neurodevelopment and Cognition
A Systematic Review

Collaborative for Health and the Environment

December 3, 2024

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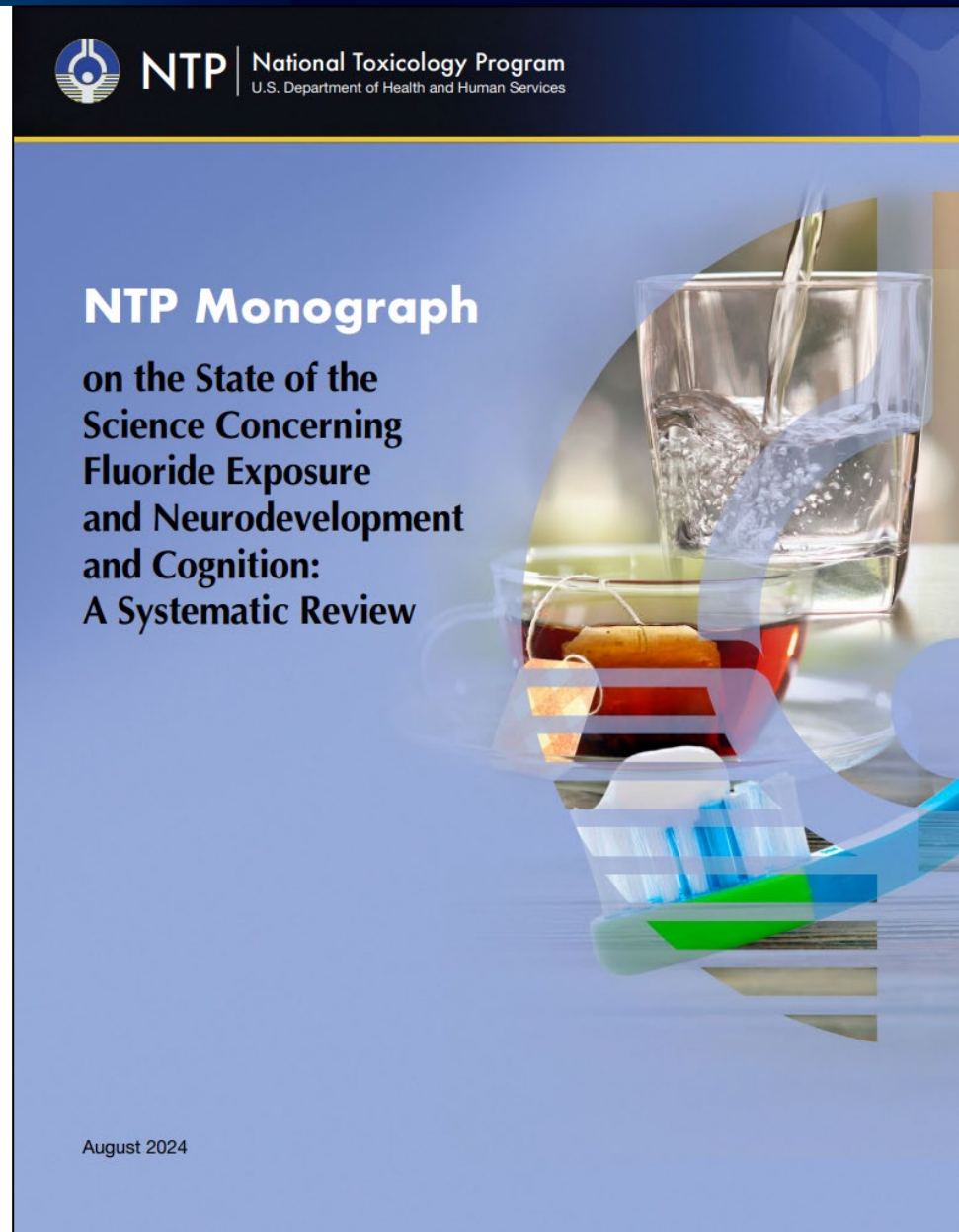
Integrative Health Assessments Branch
Division of Translational Toxicology
National Institute of Environmental Health Sciences

Talk outline

- What is fluoride? The history of U.S. water fluoridation
- NTP Monograph: Fluoride, neurodevelopment, and cognition
- Public health relevance
- Recent federal court ruling and role of the Monograph
- Questions and panel discussion



What is fluoride?

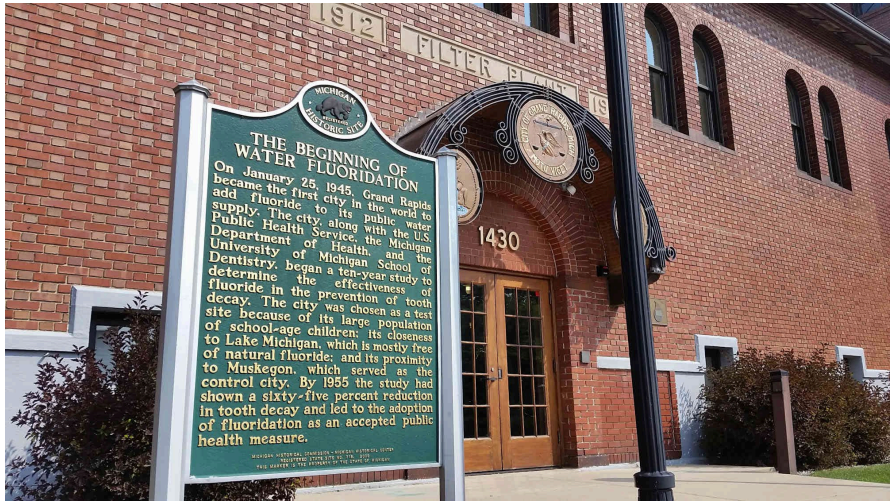
- Naturally occurring mineral
- Topical contact reduces risk of cavities
- Added to drinking water
- Many other sources of exposure

Topical sources

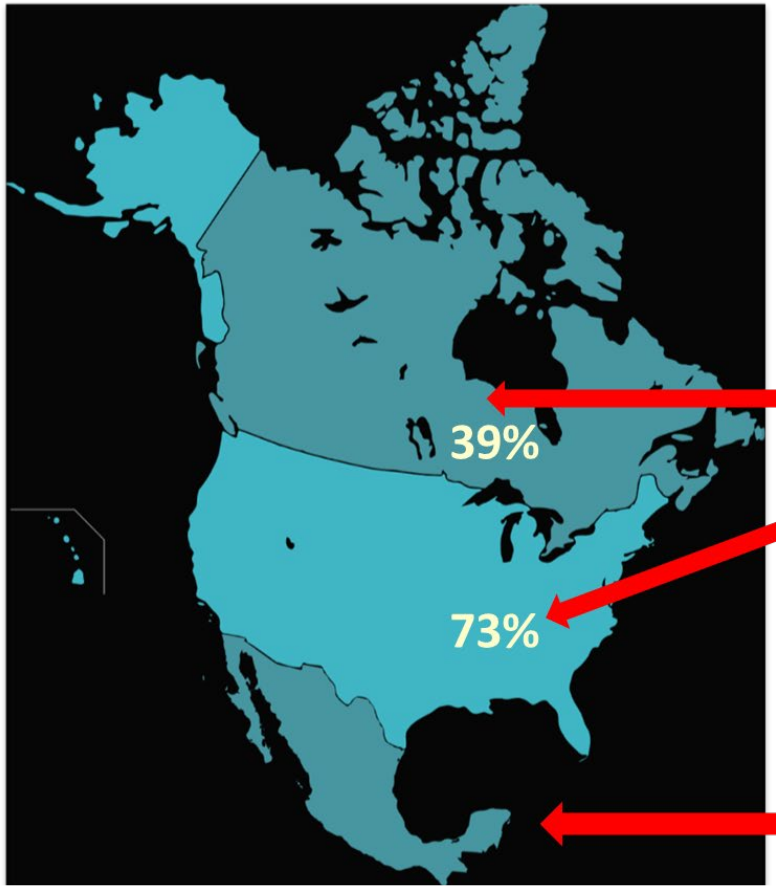
Systemic sources

History of U.S. water fluoridation

- Early 20th century researchers noticed that people living in areas with high levels of fluoride in drinking water had fewer cavities
- First added to drinking water in Grand Rapids, Michigan in 1945
- The U.S. Public Health Service (PHS) first recommended communities add fluoride to drinking water in 1962
- U.S. PHS recommends 0.7 mg/L fluoride added to drinking water
- Community water systems serve about 200 million US residents



Sources of *added* fluoride in North America



Drinking water
Recommended: 0.7 mg fluoride/L

Salt supply is fluoridated

Public Health Agency of Canada, 2017

Adverse health effects and current drinking water standards and recommendations

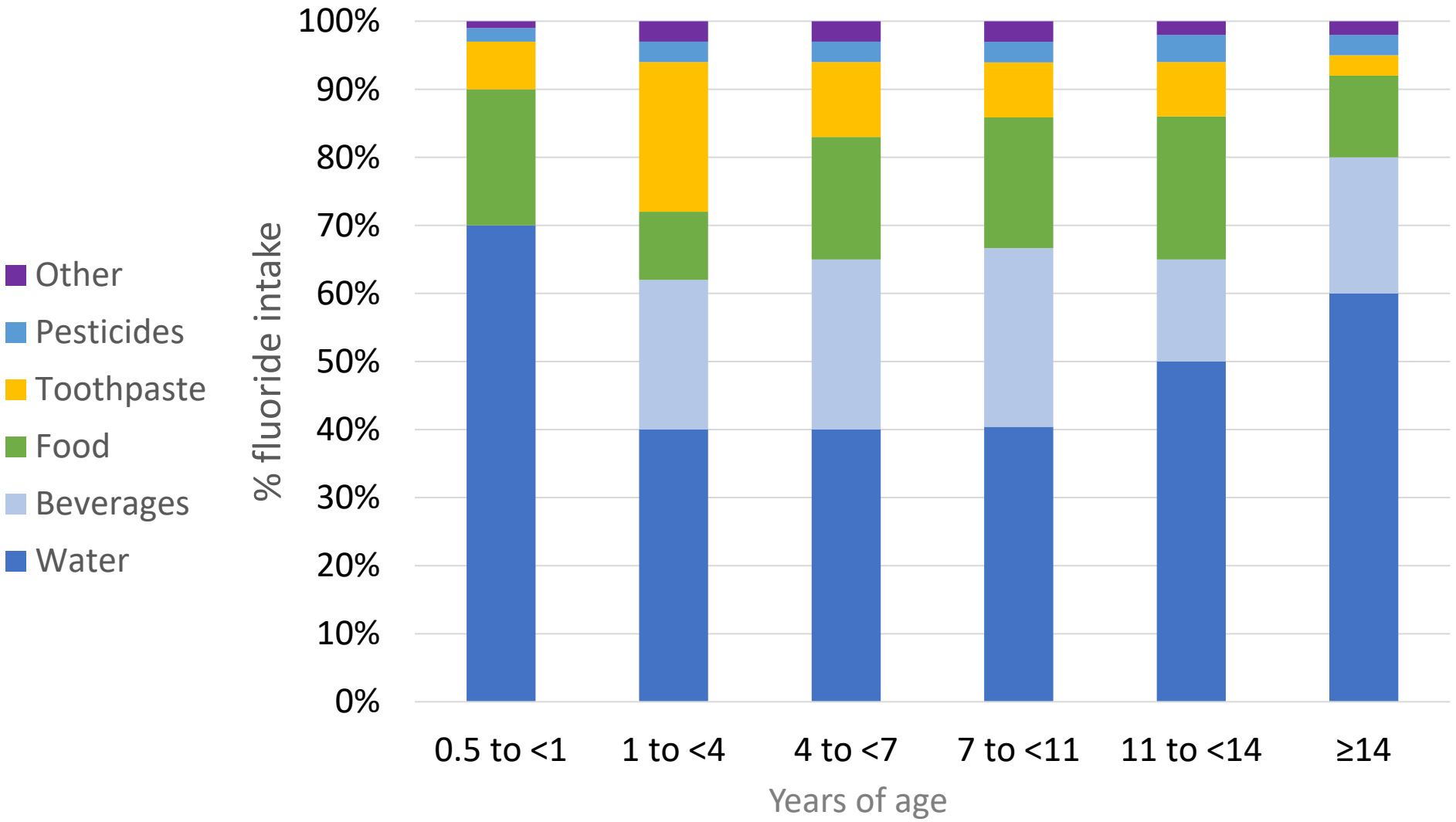
- Skeletal fluorosis
  - Bone disease caused by fluoride accumulation in the bones
  - Causes pain and tenderness of the major joints
- Dental fluorosis
  - Mild: Discoloration
  - Moderate to severe: Pitting

Dental fluorosis is the white discoloration

	Agency	Fluoride drinking water level	US residents served by CWSs above level
Standards (enforceable)	US EPA	4.0 mg/L	> 40,000
Recommendations (non-enforceable)	US EPA	2.0 mg/L	> 1.9 Million
	WHO	1.5 mg/L	> 2.9 Million
	US PHS	0.7 mg/L	>20.5 Million

CWS: Community water system
EPA: Environmental Protection Agency
WHO: World Health Organization
PHS: Public Health Service

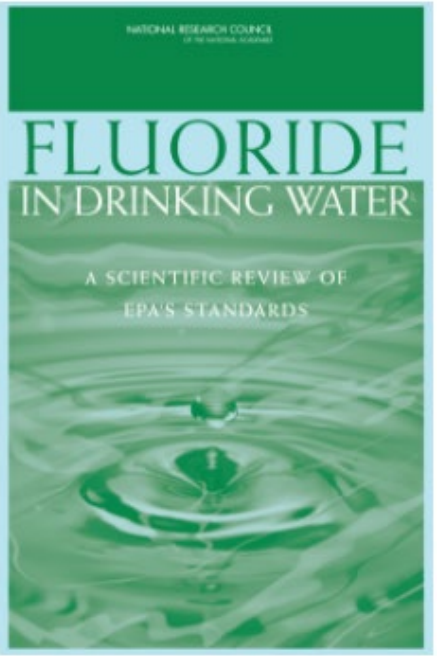
% total fluoride intake in children from various sources, by age



US EPA Fluoride: Exposure and Relative Source Contribution Analysis (2010)

Neurotoxic effects?

- **2006:** National Research Council (NRC) reported evidence of neurotoxic effects of fluoride
- Fetal and developing brains are especially vulnerable to neurotoxicants
- Concern that some pregnant women and children may be getting more fluoride than they need because they now get fluoride from many sources and the combined total intake of fluoride may exceed safe amounts
- Fetal exposure
  - Fluoride from maternal blood crosses placenta
  - Fluoride stored in bone and remobilized into bloodstream during pregnancy
- Formula-fed infants residing in fluoridated communities:
  - 3-4 times greater exposure to fluoride than adults on a per body-weight basis
  - ~70-fold higher fluoride intake than exclusively breastfed infants

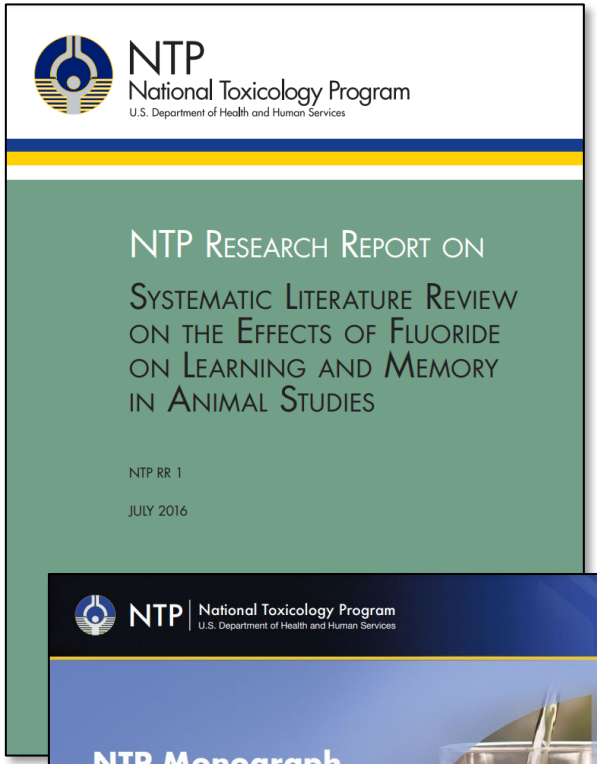


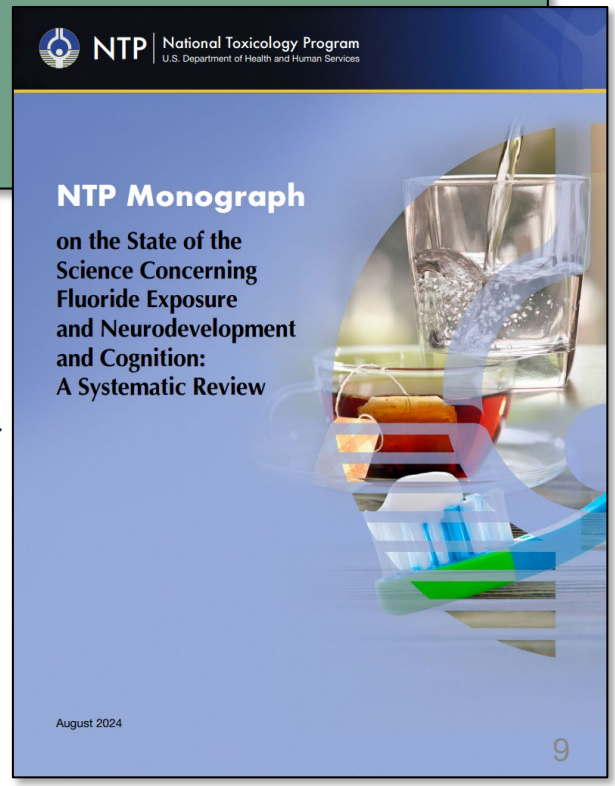
Fluoride as a topic for evaluation at the National Toxicology Program (NTP)

- **2015:** Topic of fluoride exposure & adverse health effects nominated to NTP
- **2016:** NTP Monograph (animal studies only) published
  - Systematic review of animal studies found *low to moderate* evidence of adverse effects on learning and memory

2nd NTP systematic review to evaluate potential neurodevelopmental and cognitive effects of fluoride in the human, animal, and mechanistic/*in vitro* literature

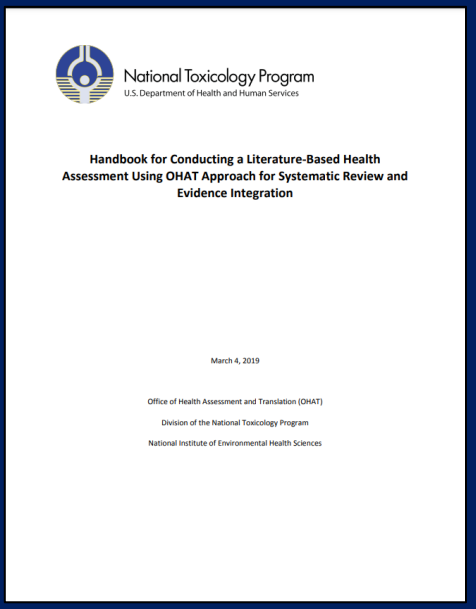
Published August 2024





What is systematic review?

- Transparent and rigorous method for identifying, evaluating, and summarizing every single relevant study published on a topic
- Look for patterns across a body of evidence, and develop conclusions based on the best available evidence
- **OHAT approach to systematic review**, developed in 2014, is a framework for systematic review and evidence integration across human, animal, mechanistic studies
  - Developed to address challenges with reproducibility, transparency
  - Leading edge of bringing systematic review methodology to toxicology and environmental health
- Given **importance and scrutiny** of public health decisions, adherence to standardized methods is essential


National Toxicology Program
U.S. Department of Health and Human Services

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

March 4, 2019

Office of Health Assessment and Translation (OHAT)

Division of the National Toxicology Program

National Institute of Environmental Health Sciences


Research

Systematic Review and Evidence Integration for Literature-Based Environmental Health Science Assessments

Andrew A. Rooney, Abee L. Boyles, Mary S. Wolfe, John R. Bucher, and Kristina A. Thayer

Office of Health Assessment and Translation, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA

Introduction

Methods

OHAT Handbook: https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf

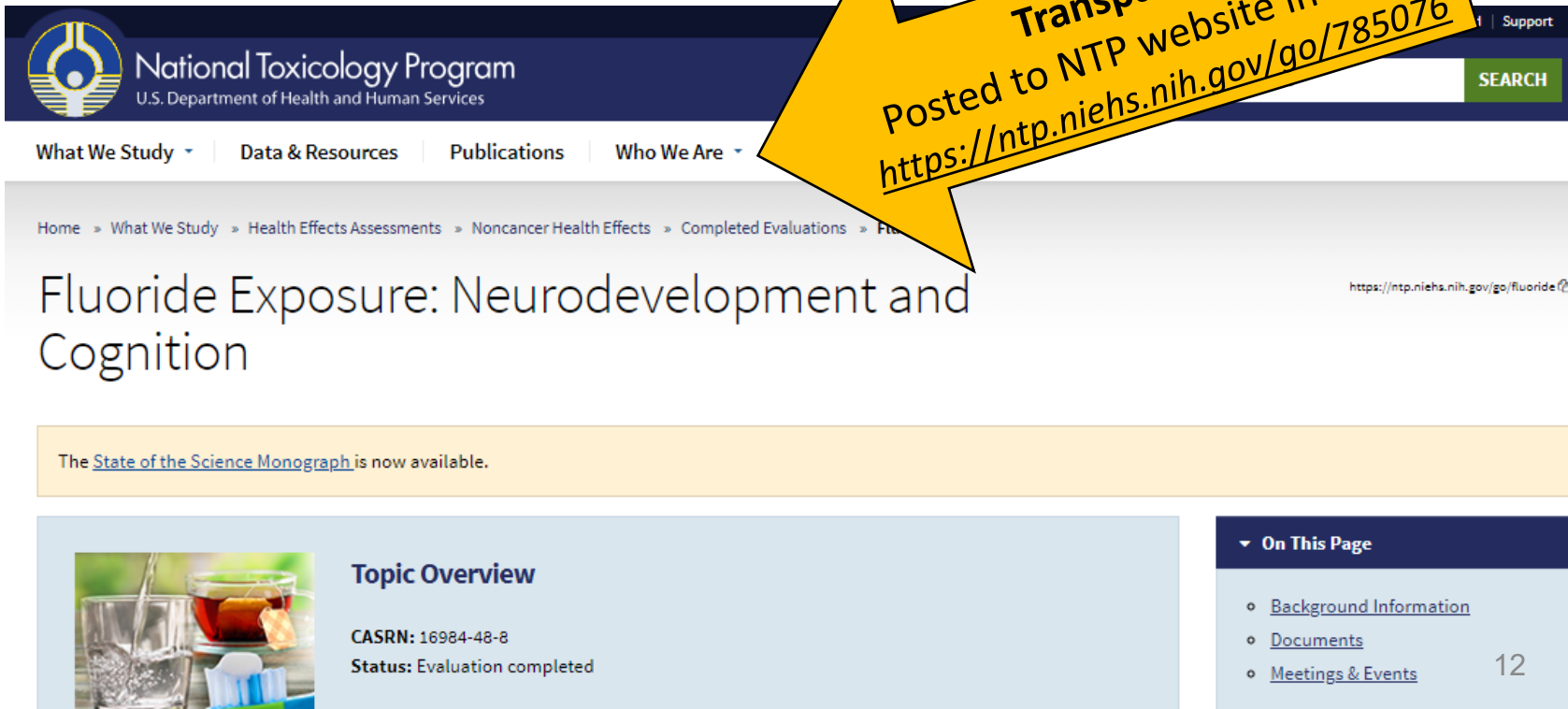
OHAT approach to systematic review

- Systematic Review
  - Planning and protocol development
  - Identify evidence
    - Comprehensive literature search
    - Literature screening
  - Evaluate evidence
    - Extract data
    - Risk of bias assessment

OHAT approach to systematic review

- **Systematic Review**
  - **Planning and protocol development** →
    - Refined research question, developed detailed protocol with input from technical experts
    - Formal peer review of protocol
  - Identify evidence
    - Comprehensive literature search
    - Literature screening
  - Evaluate evidence
    - Extract data
    - Risk of bias assessment

Transparency
Posted to NTP website in 2017
https://ntp.niehs.nih.gov/go/785076



OHAT approach to systematic review

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    - **Comprehensive literature search**
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- Comprehensive literature search of eight databases through May 1, 2020 (***Addendum update through October 2023***)
  - BIOSIS, EMBASE, PsychINFO, PubMed, Scopus, Web of Science, CNKI, and Wanfang
  - Peer reviewed articles, no language restrictions
- References screened for relevance (2 independent reviewers)
  - Selection based on predefined Population, Exposure, Comparator, and Outcome (PECO) criteria to avoid bias

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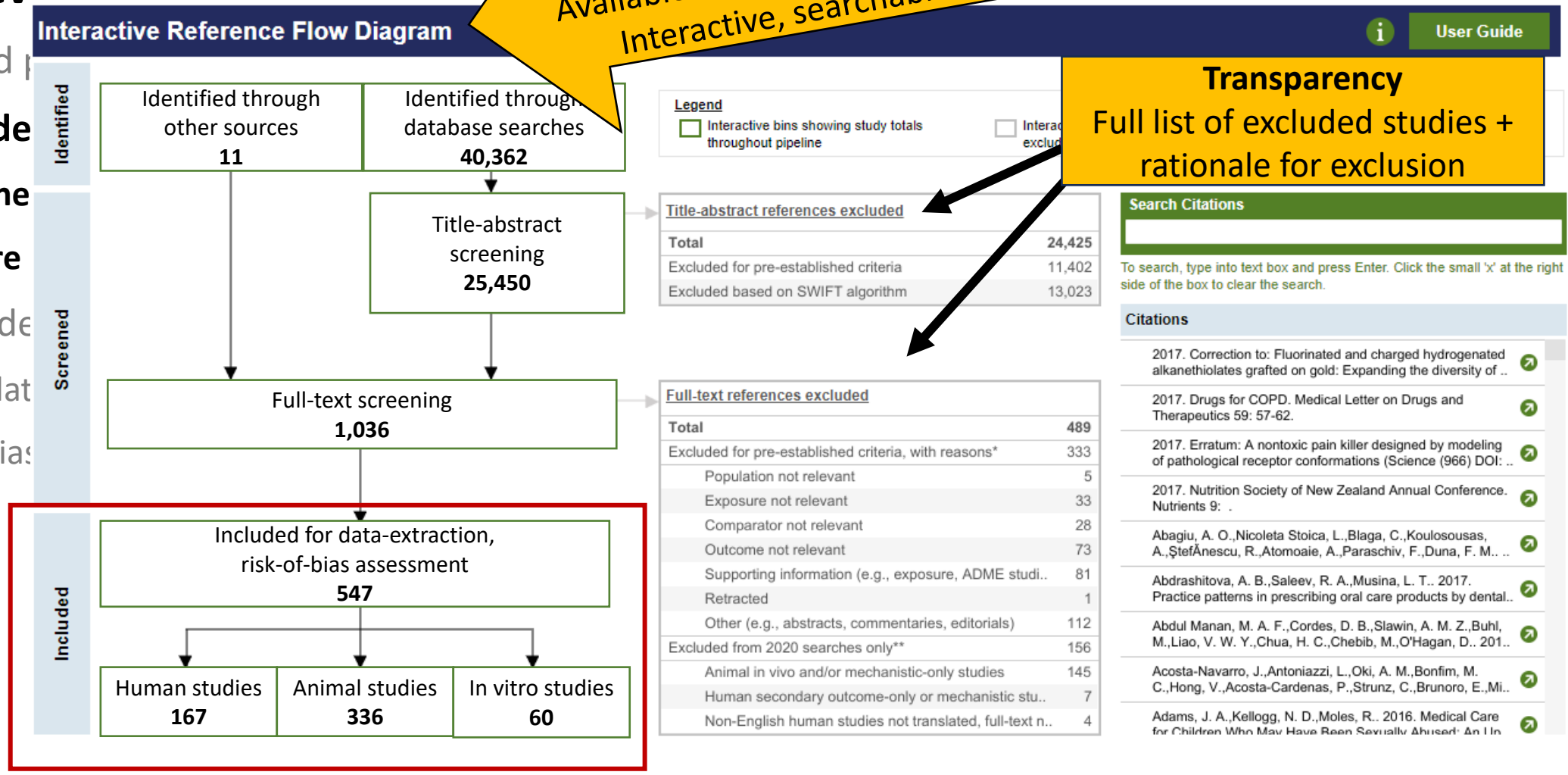
Transparency
Available through NTP website
Interactive, searchable

Transparency
Full list of excluded studies + rationale for exclusion

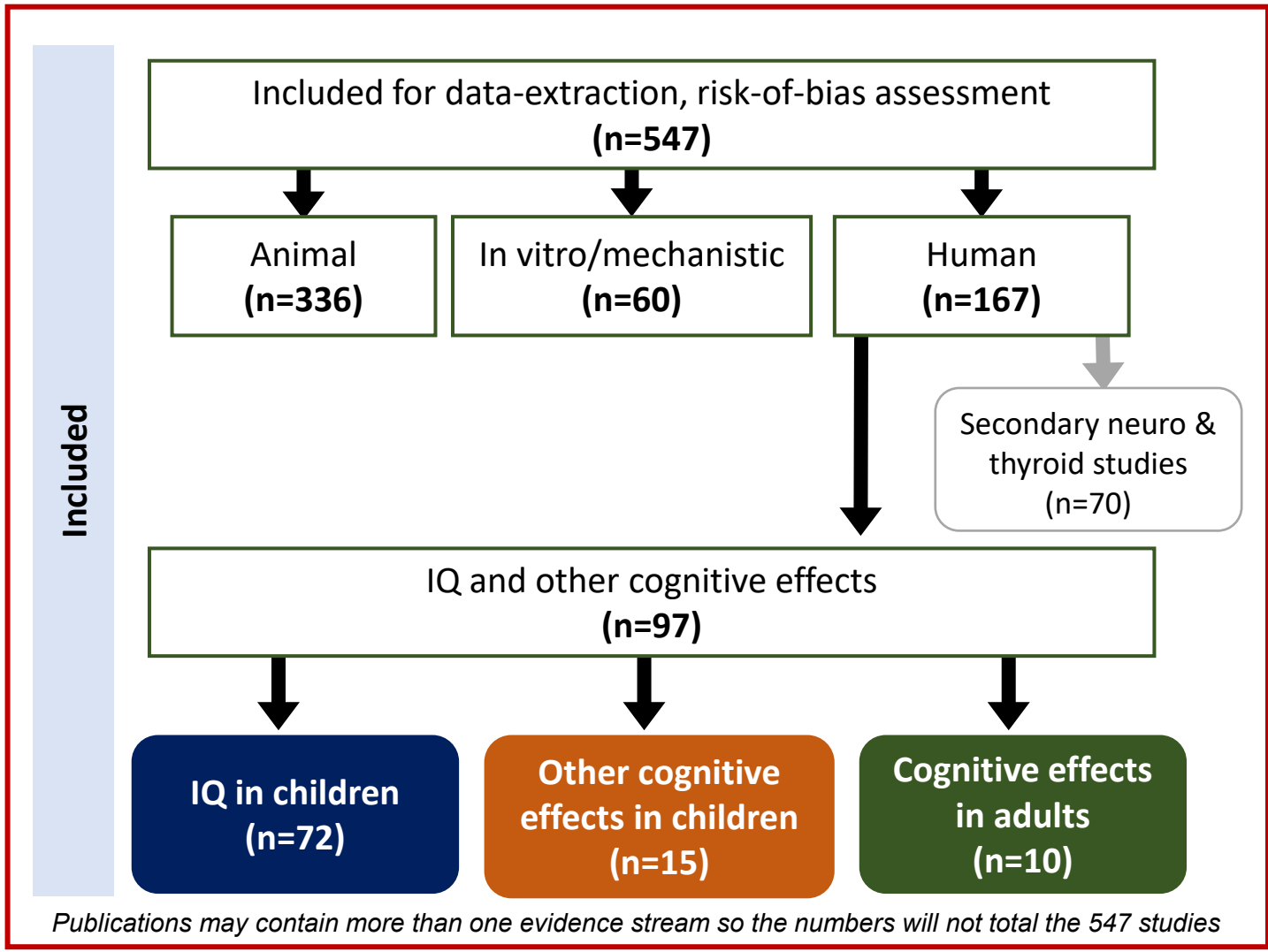


https://hawcproject.org/summary/visual/assessment/405/Figure-2/

Systematic review focuses on the human studies

- 547 human, animal, mechanistic/ in vitro studies considered relevant
- Experimental animal learning and memory data ***inadequate*** to inform assessment of neurodevelopment and cognitive effects in humans
- In vitro/mechanistic studies too heterogeneous and limited to make determination on biological plausibility (e.g., changes in thyroid hormone)

Details for each evidence stream available in NTP Monograph



OHAT approach to systematic review

- **Systematic Review**
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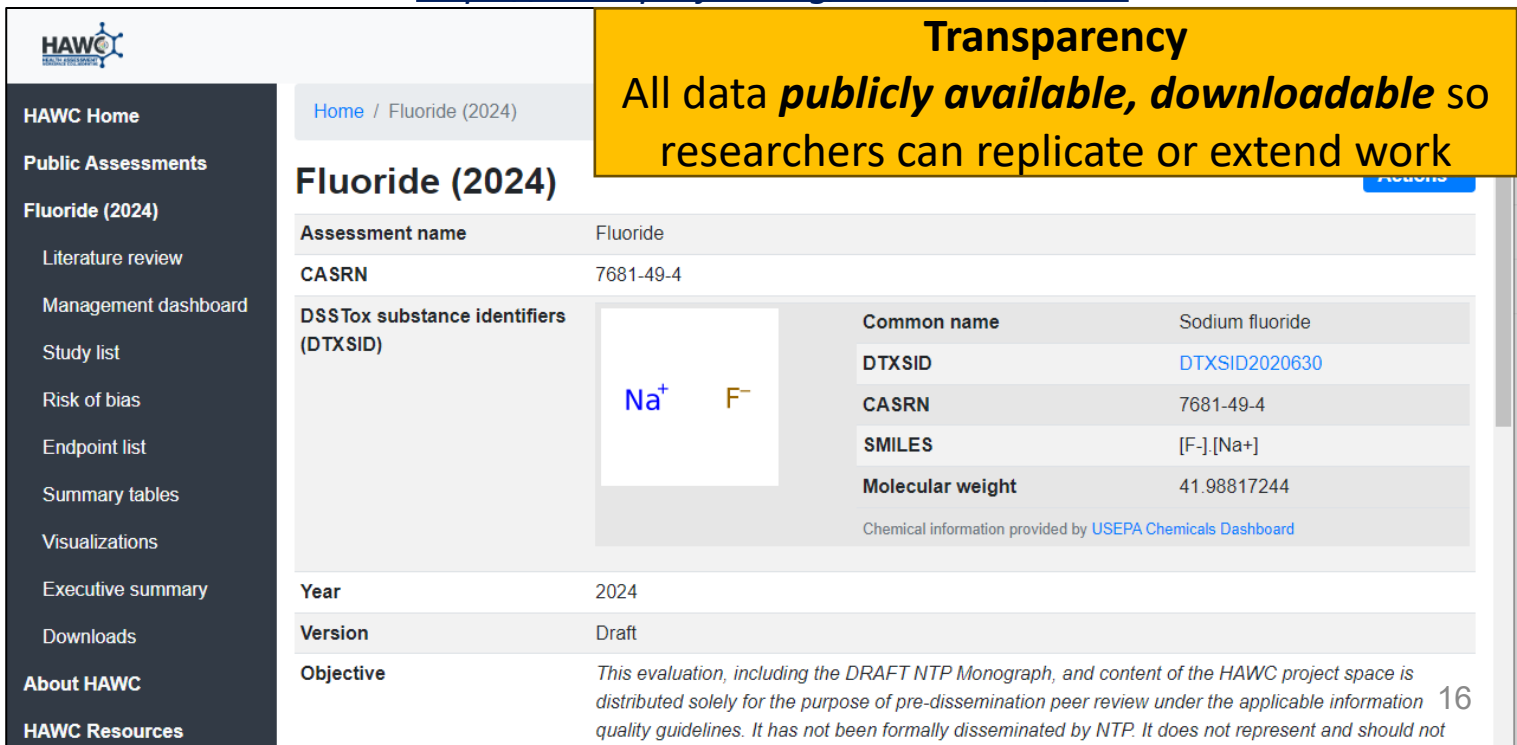
  - **Evaluate evidence**
    - **Extract data**
    - Risk of bias assessment

- Open source, web-based application for data extraction and visualizations
- Health Assessment Workspace Collaborative (HAWC) developed at DTT, NIEHS (*Shapiro et al., 2018)*

https://hawcproject.org/assessment/405

Transparency
All data ***publicly available, downloadable*** so researchers can replicate or extend work



OHAT approach to systematic review

- **Systematic Review**
  - Planning and protocol development
  - Identify evidence
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  - **Evaluate evidence**
    - Extract data
    - **Risk of bias assessment**

- Evaluate **7 risk-of-bias domains**
  - ✓ Confounding bias
  - ✓ Exposure characterization
  - ✓ Outcome assessment
  - Selection bias
  - Attrition bias
  - Selective reporting
  - Other (e.g., statistical analyses)

Key domains: Greatest potential to impact results of a study

Risk of Bias Ratings	
- -	Definitely high
-/NR	Probably high or NR
+	Probably low
++	Definitely low

NR: Not reported

Transparency
Interactive risk of bias ratings and rationale for each individual study available in HAWC

https://hawcproject.org/assessment/405

Identify “high quality” and “low quality” studies

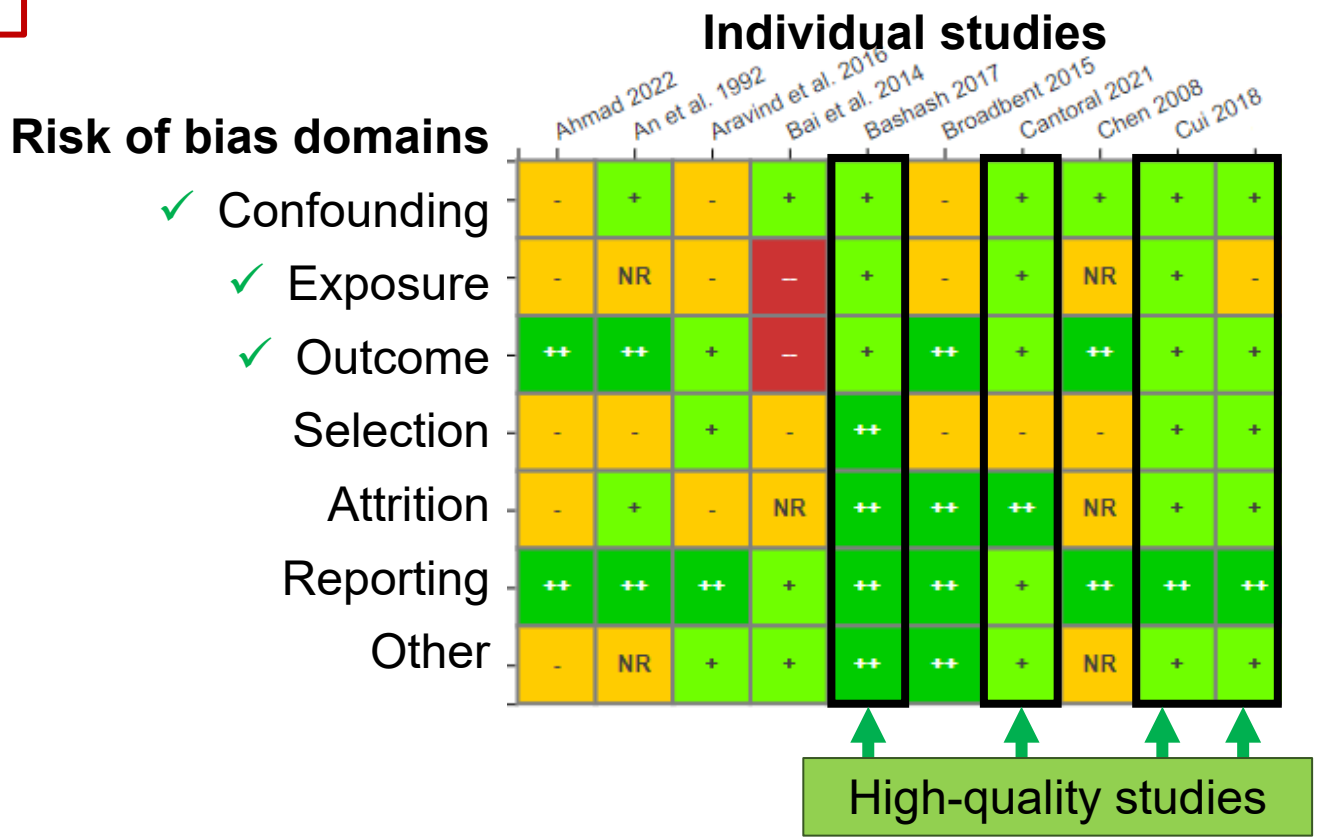
High quality studies represent **the best evidence**, and are basis for the Monograph’s conclusions

- A high-quality study’s **risk of bias ratings** are:

+ ++	For most domains
-	No more than one in a key domain
- -	None in any domain

Risk of Bias Ratings	
- -	Definitely high
-/NR	Probably high or NR
+	Probably low
++	Definitely low

NR: Not reported

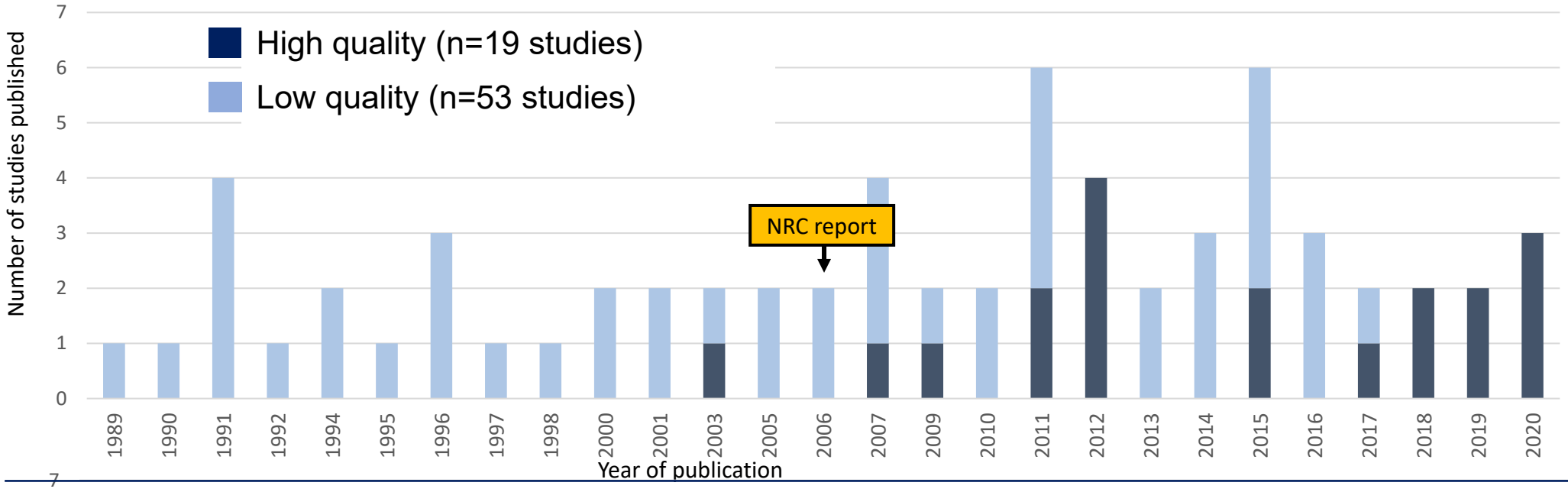


Characteristics of high-quality studies

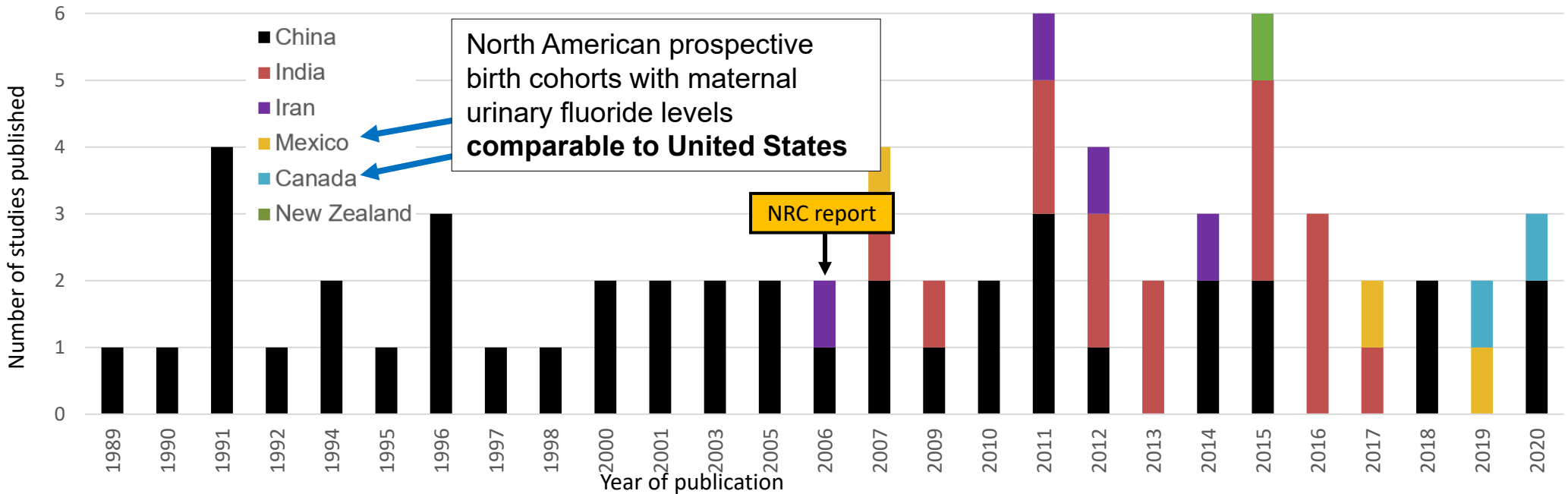
Important for determining confidence

- Most established exposure occurred prior to outcome assessment (i.e., temporality)
  - e.g., prospective cohort studies or prevalence of dental fluorosis in children, limiting study populations to children who lived in an area for long periods of time
- Used IQ tests that were appropriate for the population being studied, outcome assessors were blind to fluoride exposure status
- Accounted for **key confounders** (e.g., age, sex, socioeconomic status) including potential co-exposures to other neurotoxins (e.g., arsenic, lead intake)
- Used individual-level exposure assessment measures (e.g., urine or water)
  - Or, if using group-level data, confirmed regions being compared had differences in fluoride exposure
- Used appropriate sampling techniques for study populations and statistical approaches for analyses
  - e.g., stratified multistage random sampling, regression techniques that account for clustering

Study quality and year of publication in studies of fluoride exposure and children's IQ

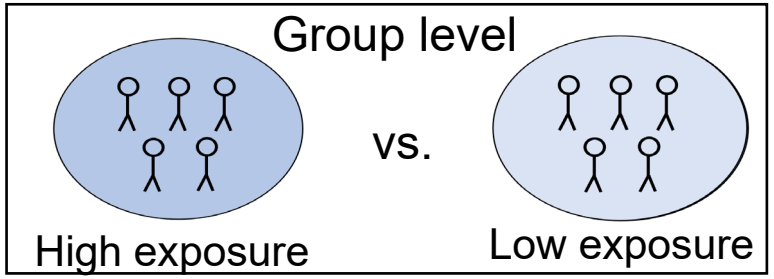


Study location and year of publication in studies of fluoride exposure and children's IQ

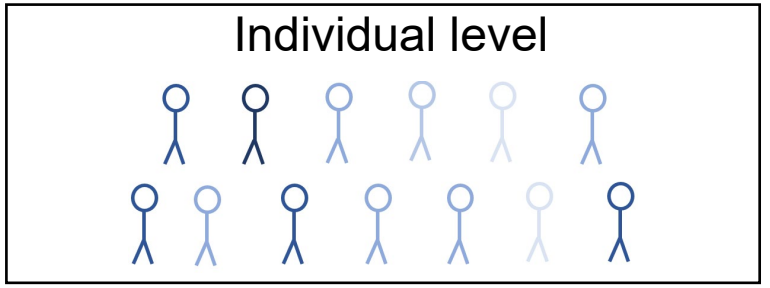


NRC: National Research Council

Exposure data fell into two general categories



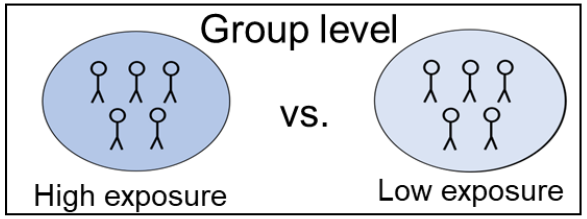
- Reported group-level exposure measures
- Compared mean IQ of children living in “high” fluoride areas to children living in “low” fluoride areas
- Measures included
  - Village or area of residence (endemic vs. non-endemic)
  - Drinking water
  - Children’s urine
  - Severity of dental fluorosis
  - Coal burning



- Reported individual-level exposure measures
- Reported regression coefficients for change in children’s IQ per 1 mg/L increase in urinary fluoride levels
- Measures included
  - Children’s urine
  - Maternal urine
  - Drinking water
  - Fluoride intake
  - Serum

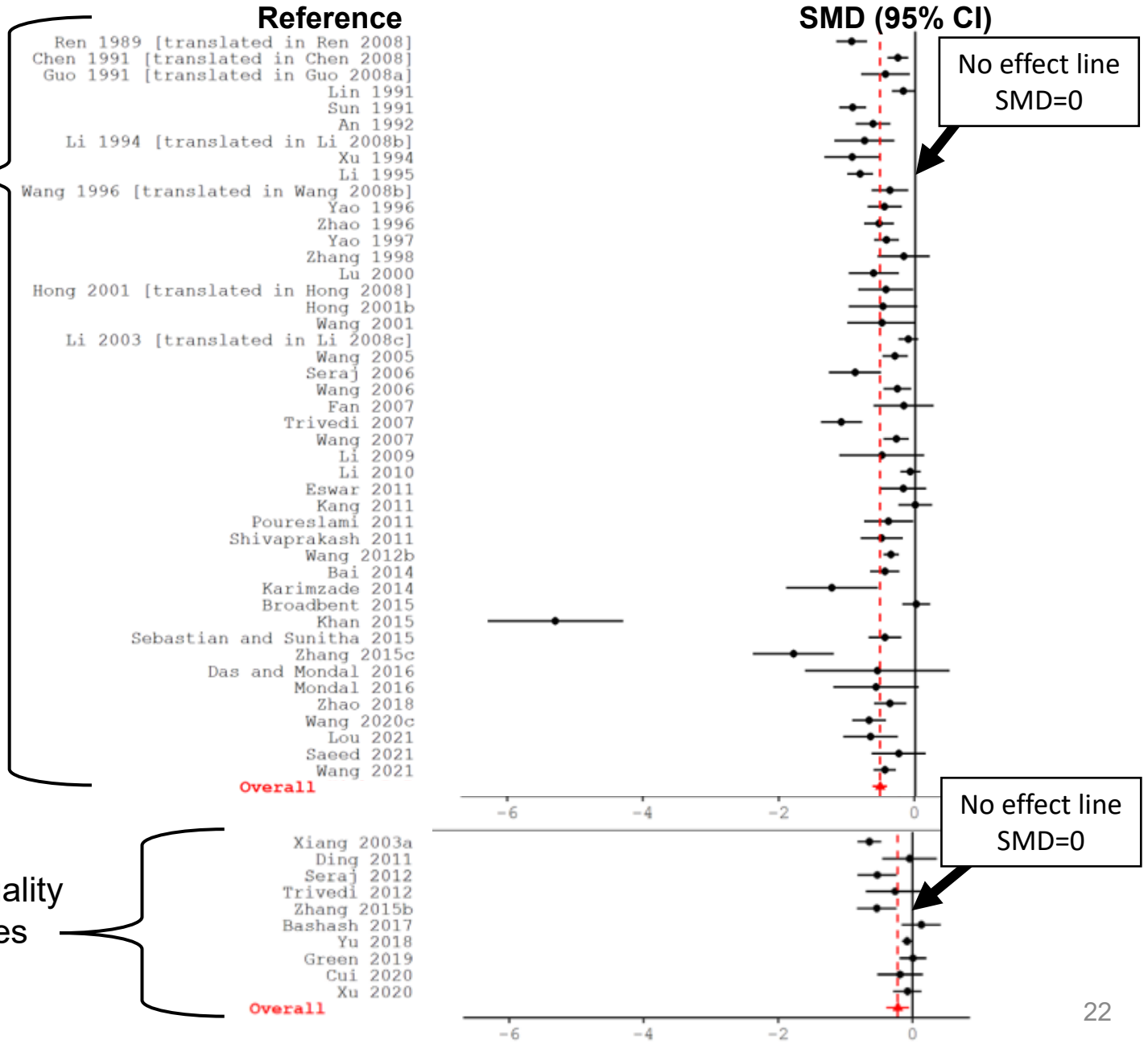
Consistency across high- and low-quality studies

Group-level data



- Standardized mean difference (SMD) for studies comparing children's IQ in a "high" fluoride exposure area vs. a "low" fluoride exposure area

Children in high fluoride communities have statistically significantly **lower IQ**

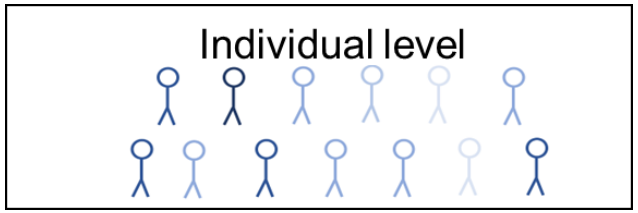


CI: Confidence intervals

Not all high-quality studies reporting group level data are displayed (e.g., studies that did not report data in a way that could be plotted as an SMD)

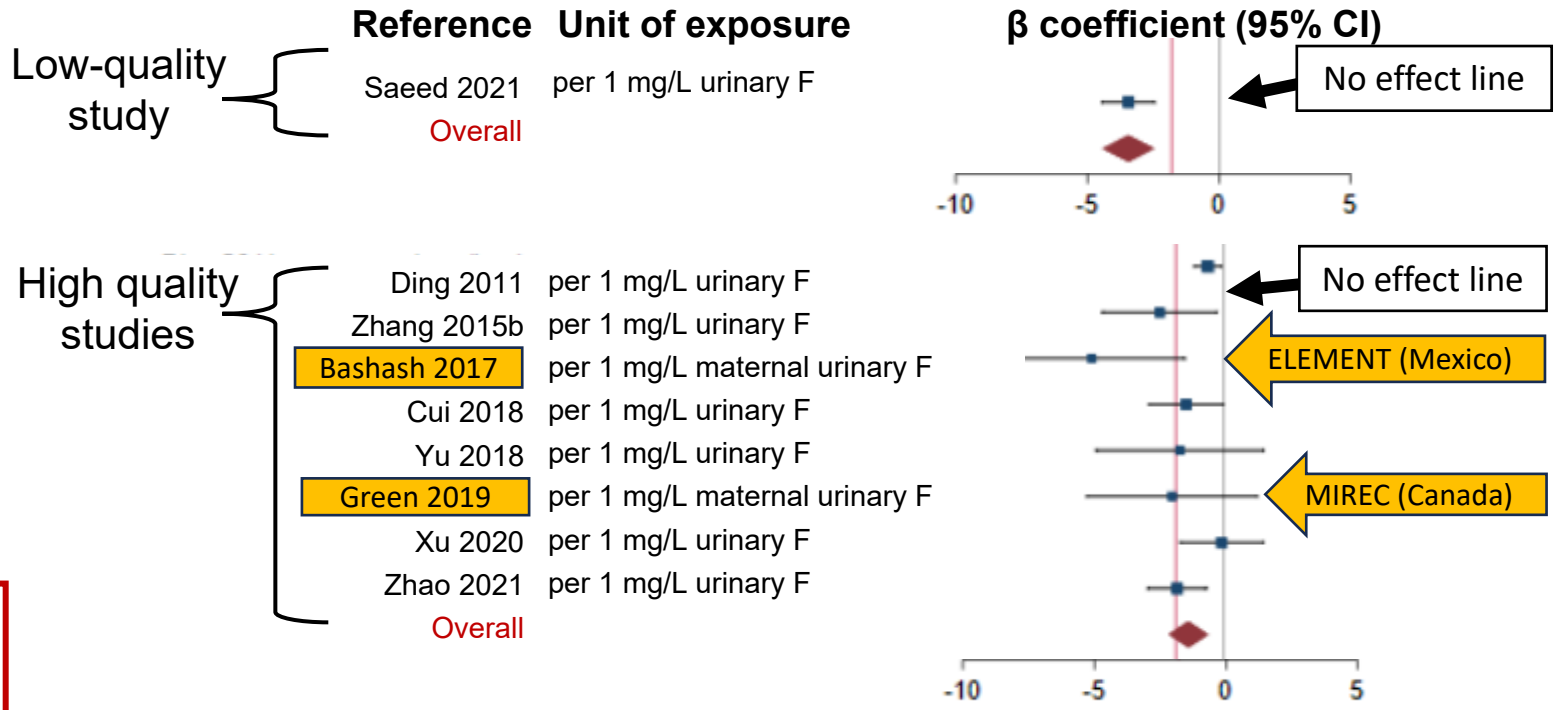
Consistency across high- and low-quality studies

Individual-level data



- Regression coefficients (β) and 95% CIs for change in children's IQ per 1 mg/L increase in maternal or children's urinary fluoride

For every 1 mg/L increase in urinary fluoride there is a statistically significant **decrease children's IQ**



ELEMENT and MIREC cohorts reported maternal urinary fluoride levels **comparable to the United States** (*Ugyturk 2020, Malin 2024*)

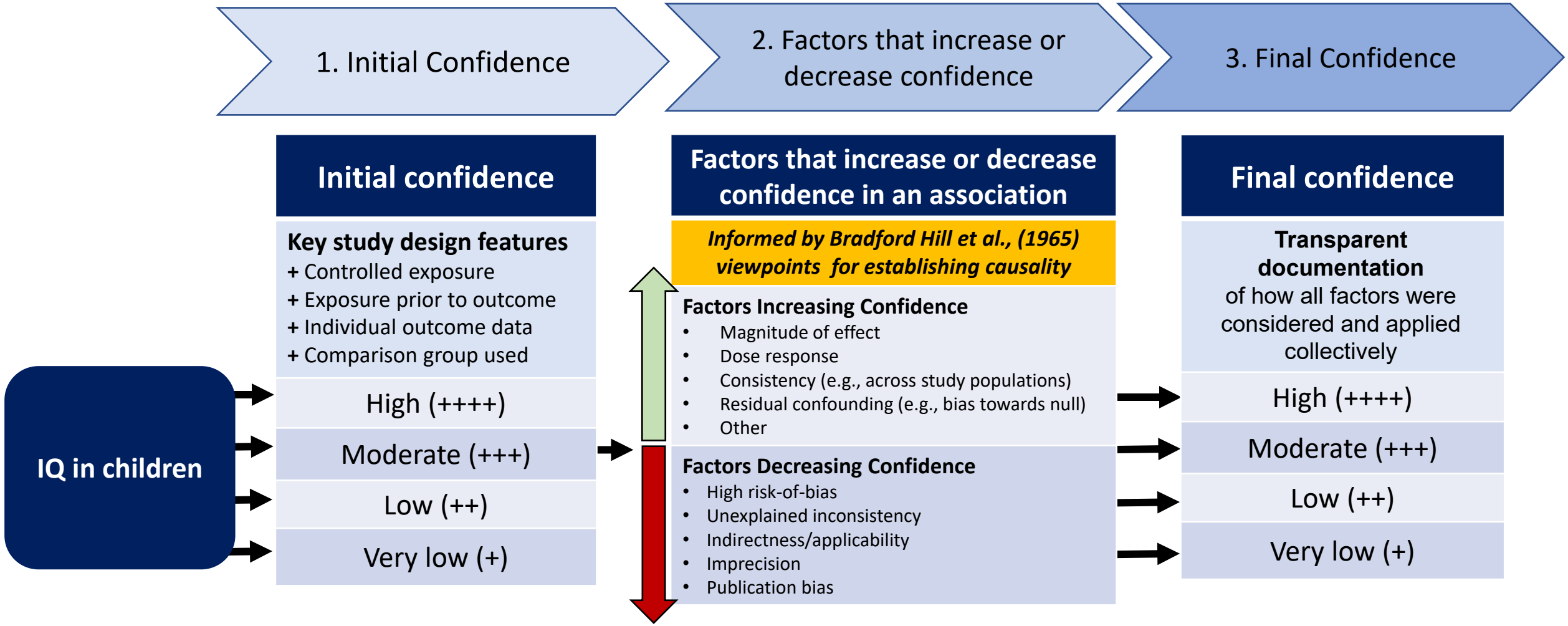
- Green et al 2019 (MIREC): β = **-1.95** (95% CI: -5.19, 1.28)
- Bashash 2017 (ELEMENT): β = **-5.16** (95% CI: −9.12, −1.19)

Interpretation: Per 1 mg/L increase in maternal urinary fluoride, → 2 to 5 point decrease in children's IQ

Confidence ratings

- Rate confidence in bodies of evidence that overall findings ***reflect the true exposure-effect relationship***
- Four-point scale:
  - High confidence
  - Moderate confidence
  - Low confidence
  - Very Low confidence
- Performed for bodies of evidence on outcome basis
- Considers principles that are ***consistent with causation***

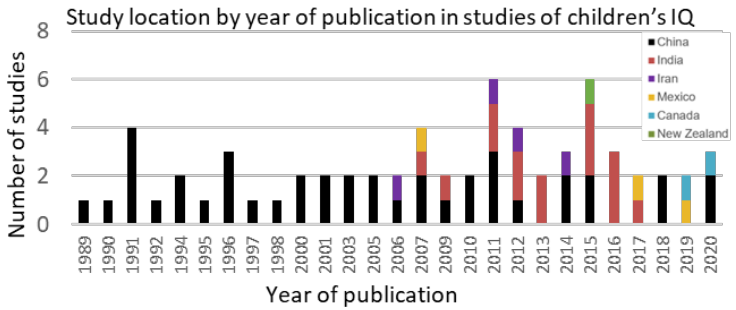
3 steps for determining confidence

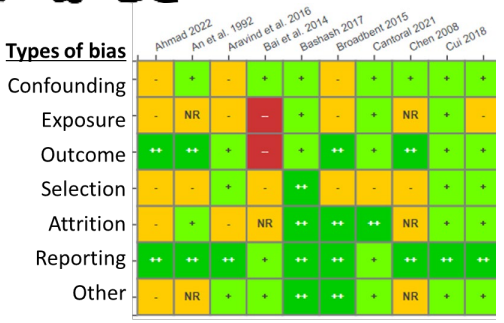


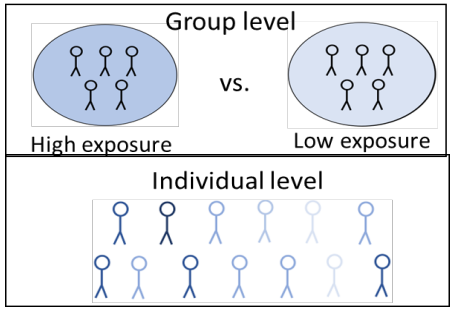
Considerations for confidence ratings

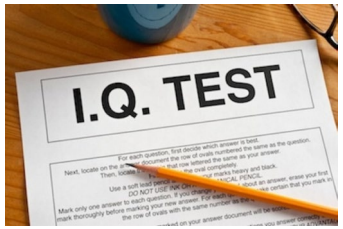
Studies of fluoride exposure and children's IQ

- Consistent inverse association across:
  - 18 of 19 high quality studies
  - 46 of the 53 low quality studies
  - Study populations from different countries
  - Study designs (cross-sectional, prospective cohort)
  - Risk of bias ratings
  - Exposure matrices (water and urine)
  - Type of exposure data (group and individual level data)
  - Timing of exposure (pre- and post-natal)
  - Outcome assessment type (different types of IQ tests)
- Heterogeneity in methods, NOT heterogeneity in results
- Each level of consistency **strengthens** overall confidence
- Determined confounding could not explain these results *(see NTP Monograph for details)*









NTP Conclusion:

Moderate confidence that

higher fluoride exposure is associated with lower IQ children

Extensive peer review

2019–2020

National Academies of Science, Engineering, Medicine (NASEM) committee reviewed initial (2019) & revised (2020) drafts

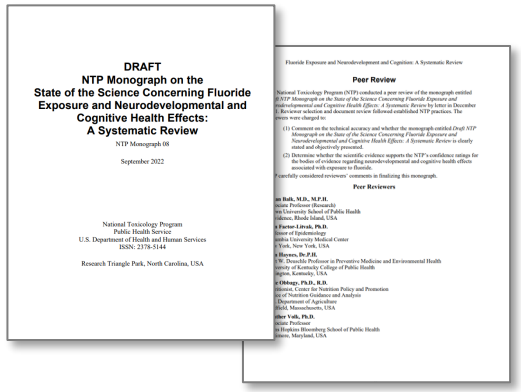
NTP revised Monograph in response to these reviews

2021

External peer review by 5 independent reviewers of 2021 draft NTP Monograph (typical NTP peer review process)

Both **NASEM reviews** & author responses provided

Reviewers ***unanimously*** agree with NTP's conclusions



2022

DTT Scientific Director approves NTP Monograph to be published (May 2022)

NTP/NIEHS Director asks NTP Board of Scientific Counselors (BSC) to review authors' responses to external peer review & *interagency comments on Monograph & meta-analysis (MA)

2023

NTP BSC working group review of author responses to external peer review & *interagency comments on Monograph & MA

Both **NASEM reviews** & author responses provided

Issued recommendations for language refinement & clarification

No major issues identified with methods, analyses, conclusions

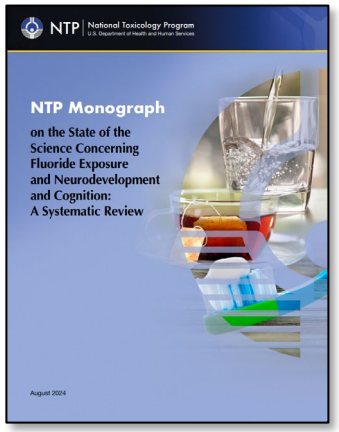
Encouraged rapid publication

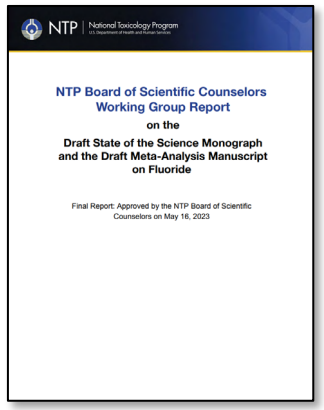
Authors respond to all NTP BSC comments

2024

Final publication
August 2024

(MA in press)





*Agencies and offices that provided comments on Monograph & MA

Office of the Director, NIH
Office of the Assistant Secretary of Health (OASH)
Food and Drug Administration (FDA)
Centers for Disease Control (CDC)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute of Child Health and Development (NICHD)

Of note…

- Final confidence conclusions based primarily on high-quality studies (i.e., the best evidence)
  - Consideration of low-quality studies does not decrease confidence in overall body of evidence
- Conclusions based primarily on non-US studies where total fluoride exposure approximated *>1.5 mg/L fluoride in drinking water
  - Several high-quality prospective birth cohort studies with maternal urinary fluoride levels comparable to the United States

  **>1.5 mg/L refers to WHO Drinking Water Guideline of 1.5 mg/L; chosen to describe "higher" fluoride exposure in the NTP Monograph based on an overall assessment of the epidemiology literature; represents a useful total fluoride exposure equivalent metric (no alternative safety guidelines for total fluoride exist)*
- Review ***does not***
  - Evaluate benefits of fluoride or provide a risk/benefit analysis
  - Address whether ***sole exposure*** to fluoride at 0.7 mg/L in drinking water is associated with neurodevelopment and cognitive effects
- Targeted research that prospectively examines the association between fluoride exposure and children's IQ in optimally fluoridated areas of the United States would add clarity to the existing data at lower levels

Exposure considerations

- Fluoride in drinking water
  - Provides useful estimates of long-term population exposures
  - May underestimate total exposure because it does not capture the amount of water ingested or other sources of ingested fluoride
- Fluoride in urine
  - Biological measure that captures individual's total fluoride exposure
  - Represents a limited (recent) time-period
  - Multiple measurements would be more robust, e.g., cohort studies with maternal urinary fluoride had multiple measures throughout pregnancy
- Small number of studies at low exposure levels
  - Limited exposure contrasts, which makes it more difficult to detect a true effect, if it exists

Relevance to the United States

- NTP conclusions are relevant to some pregnant women, infants, and children living in the United States
  - People may have total fluoride exposures higher than levels in drinking water
  - **Over 2.9 million people** in the United States served by CWS receive drinking water with >1.5 mg fluoride/L

NEWS & FEATURES

In Millions of Homes, High Fluoride in Tap Water May Be a Concern

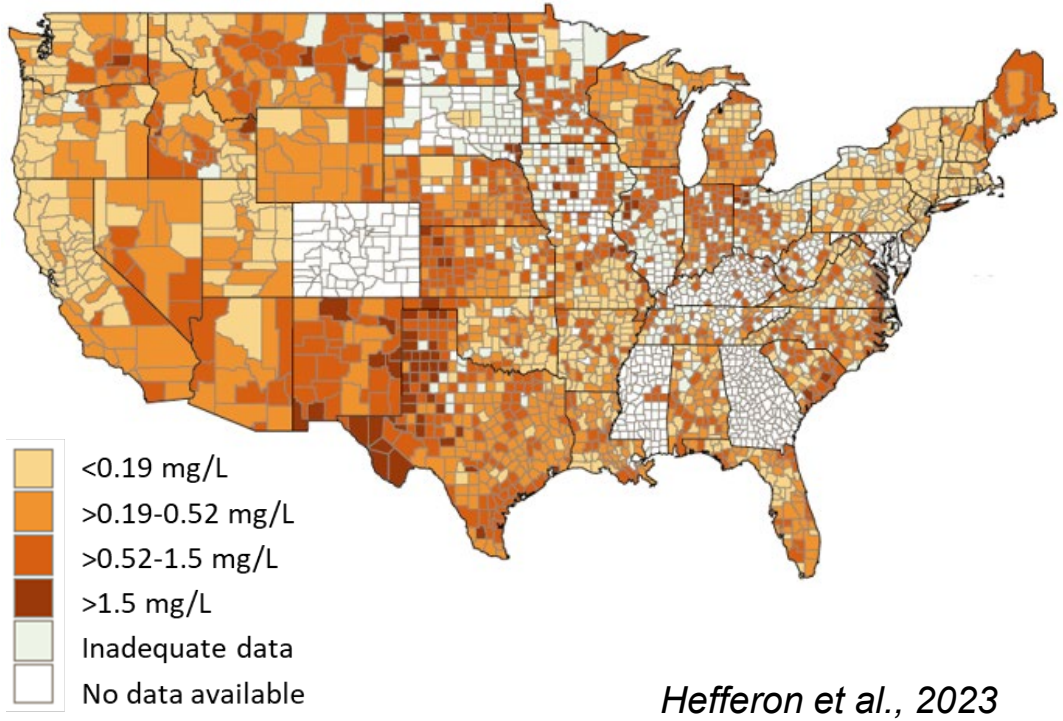
In communities across the U.S., water contains levels of fluoride some experts say could be harm developing brains.

BY MICHAEL SCHULSON
05.06.2024

Top: Water tower in Comfort, Texas. Visual: Marcus Wennrich/ iStock/Getty Images Plus

> *Lost in that debate are the roughly 3 million Americans whose water naturally contains higher concentrations of fluoride — often at levels that could have neurodevelopmental effects.*

Estimated fluoride levels in community water systems by county



Hefferon et al., 2023

Relevance to the United States

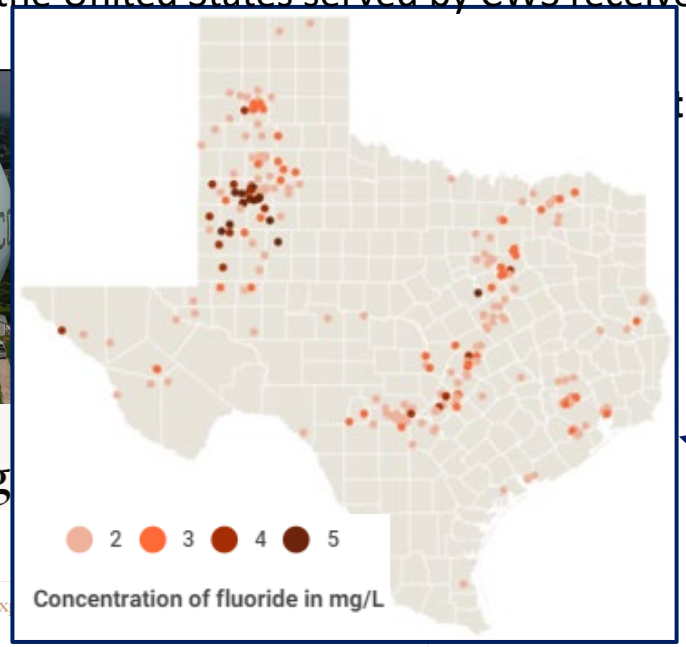
- NTP conclusions are relevant to some pregnant women, infants, and children living in the United States
  - People may have total fluoride exposures higher than levels in drinking water
  - **Over 2.9 million people** in the United States served by CWS receive drinking water with >1.5 mg fluoride/L

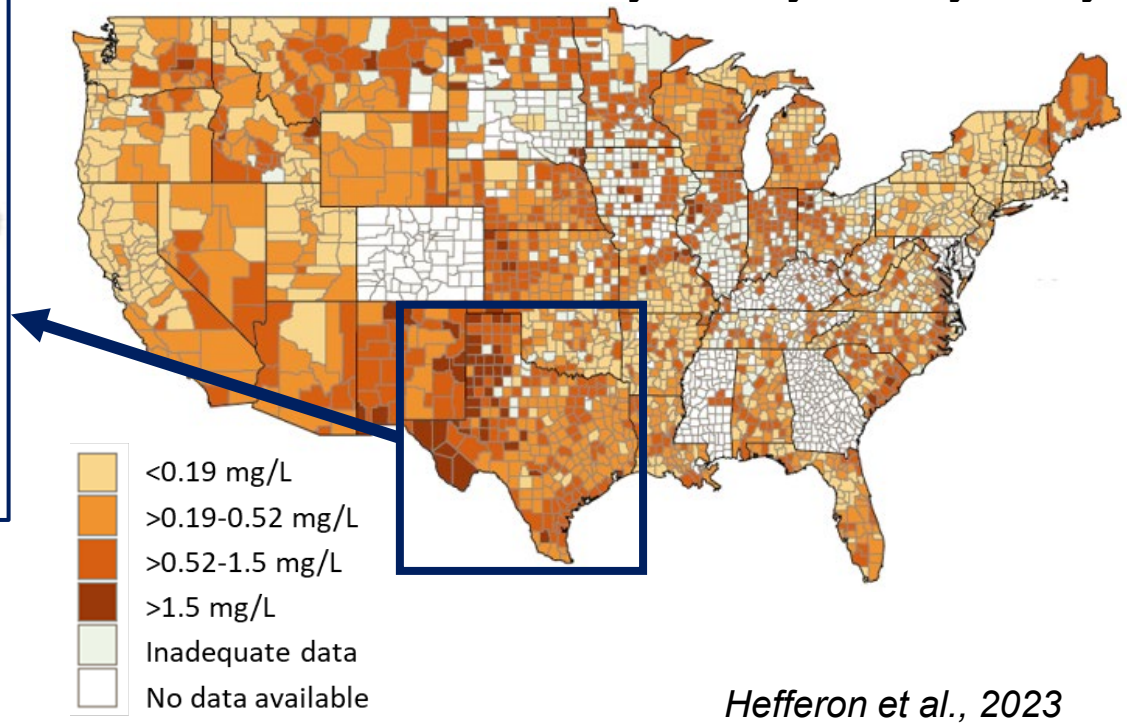
NEWS & FEATURES

In Millions of Homes, Hig
Water May Be a Concern

In communities across the U.S., water contains levels of fluoride some ex

Top: Water tower in Comfort, Texas. Visual: Marcus Wennrich/ iStock/Getty Images Plus





Hefferon et al., 2023

> *Lost in that debate are the roughly 3 million Americans whose water naturally contains higher concentrations of fluoride — often at levels that could have neurodevelopmental effects.*

Fetal and developing brains are especially vulnerable

- Benefits of fluoride are from topical contact with teeth
- No benefit from gestational exposure
- Fetal exposure:
  - Fluoride from maternal blood crosses placenta
  - Fluoride stored in bone and remobilized into bloodstream during pregnancy

The New York Times

Is Fluoridated Drinking Water Safe for Pregnant Women?

New research suggests a link between prenatal fluoride levels and behavioral issues in children. Experts are divided on the study's

By Alice Callahan and Christina Caron

May 22, 2024

- Formula-fed infants residing in fluoridated communities at higher risk of fluoride toxicity
  - 3-4 times greater exposure to fluoride than adults on a per body-weight basis
  - ~70-fold higher fluoride intake than exclusively breastfed infants
  - Retain more fluoride than breastfed infants

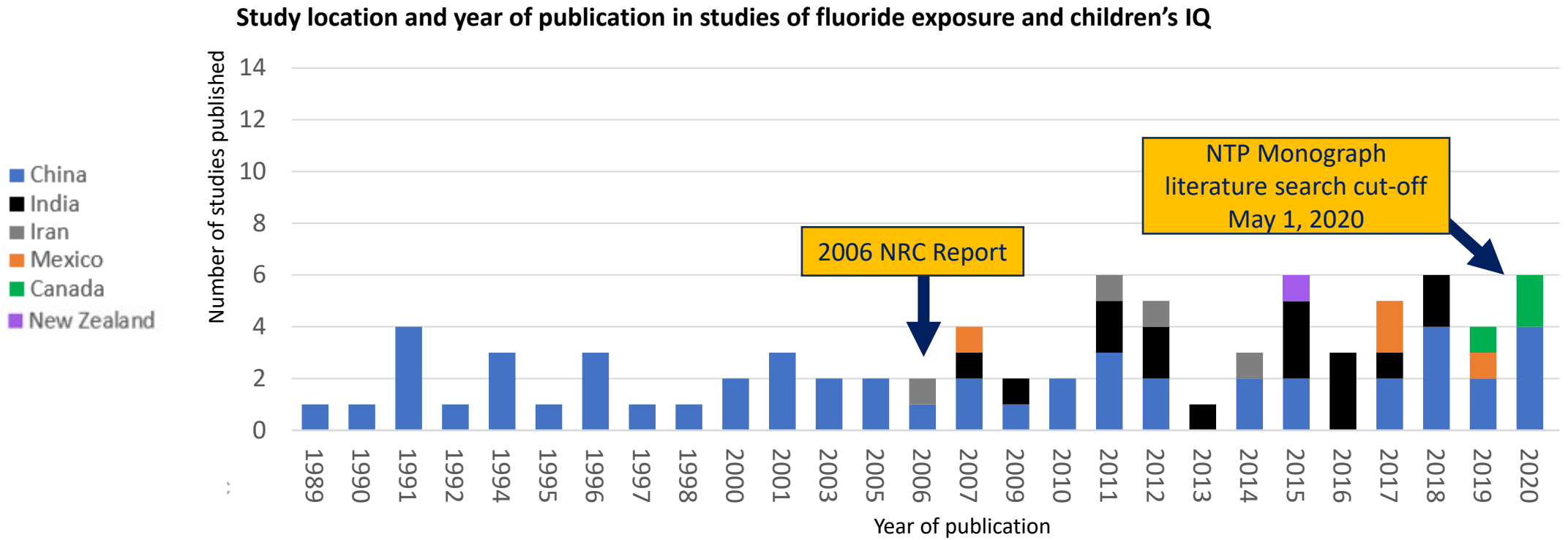
NTP Monograph played central role in recent federal trial

- What was the lawsuit about?
  - Plaintiffs petitioned EPA to evaluate fluoride in drinking water, EPA denied the petition and under Amended Toxic Substances Control Act (TSCA), Plaintiffs were entitled to a judicial review
- Monograph relied on by both Plaintiffs and EPA as a “high-quality review”
- What was the Court’s ruling?
  - On September 24, 2024, a federal district judge found that the 0.7 mg/L fluoride in drinking water, level considered “optimal” in the United States, poses an ***“unreasonable risk”*** of IQ loss in children which, under the toxics law, requires ***“a regulatory response”***
  - Finding did not conclude with certainty that fluoridated water is injurious to public health
  - Court finds the risk is ***sufficient*** to require the EPA to engage with a regulatory response, but does not dictate what that response must be, decision left to the EPA,
  - TSCA allows wide spectrum of potential risk-management measures from warning labels or public advisories to prohibiting the manufacturing and distribution of a chemical

Public health community can use the NTP systematic review as part of ongoing evaluations of the role of fluoride in drinking water

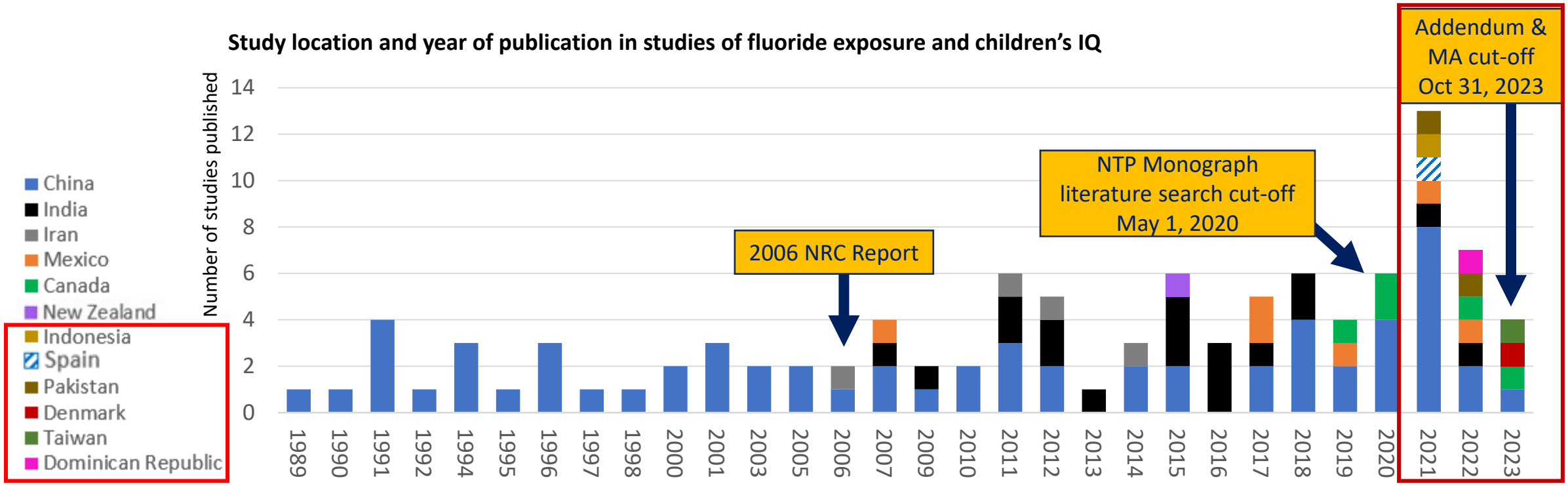
Literature since May 1, 2020?

- Addendum updated through October 2023 to match timeframe of meta-analysis (in press)



Literature since May 1, 2020?

- Addendum updated through October 2023 to match timeframe of meta-analysis (in press)
- 28 new studies
  - 12 of 12 high quality studies reported inverse associations (6 in new study populations)
  - 13 of 16 low quality reported inverse associations



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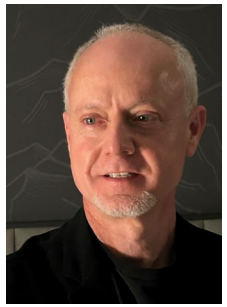

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