NTP
National Toxicology Program

Draft NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

Kyla W. Taylor, PhD
Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

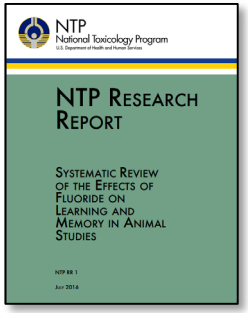
National Toxicology Program (NTP)

Office of Health Assessment and Translation

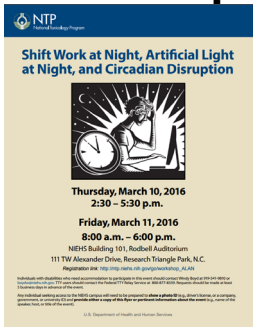
- Conduct literature-based evaluations of environmental exposures & health effects
- Consider human, animal, *in vitro* evidence
- Products include:
  - Monographs, reports, journal articles
  - **Systematic reviews**, evidence maps
- Communicated to public, government, scientific & medical communities

NTP Monographs

NTP Reports



Workshops



Literature-based evaluations

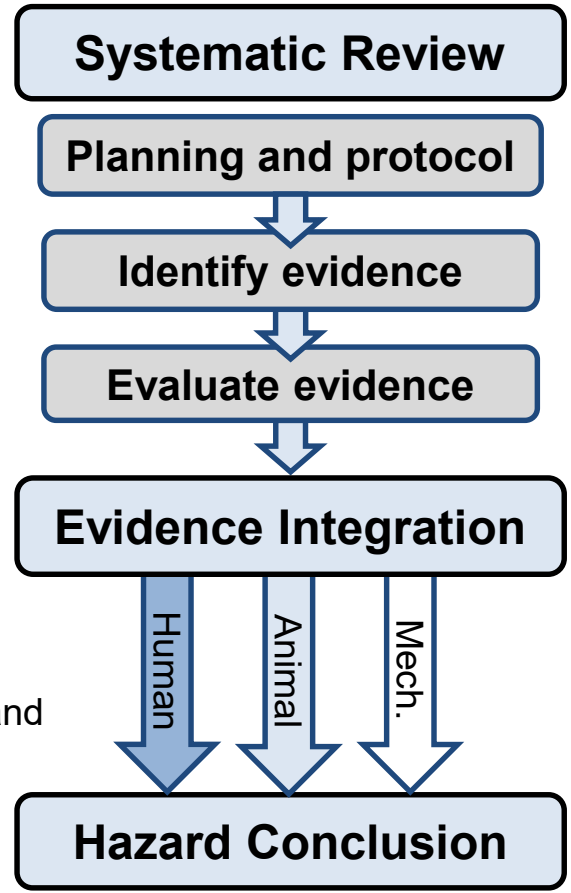
Systematic review: predefined, multi-step process to identify, select, critically assess, and synthesize evidence to answer a specific question

- Develop a protocol
- Conduct comprehensive literature search, select relevant studies
- Extract data and assess individual study quality (risk of bias)

Evidence integration: process to develop hazard conclusions by integrating evidence from human and animal studies with consideration of mechanistic data

- *Level of evidence* rating (*high, moderate, low, inadequate*) representing confidence that studies reflect the true relationship between exposure and outcome

Hazard conclusion: conclusion on evidence on 4-point scale (*known, presumed, suspected, and not classifiable*)



Background

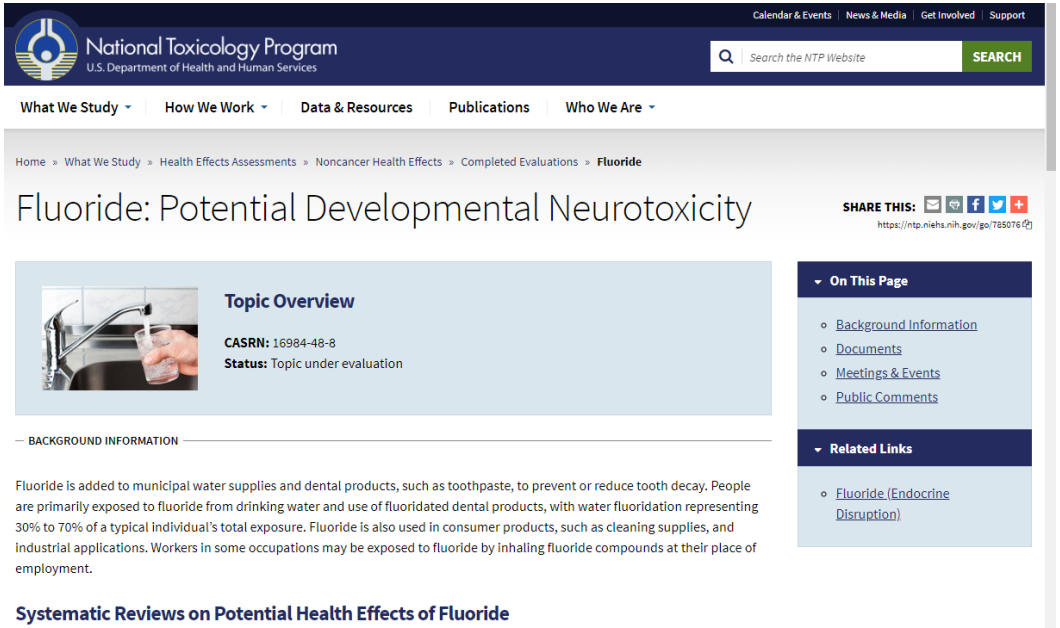
- 2006 National Research Council report
  - High number and consistency of studies suggesting fluoride might be neurotoxic warrants additional research
- 2015: Nominated to the NTP for evaluation
- 2016: NTP systematic review of experimental animal studies on potential effects of fluoride exposure on learning and memory
- 2019: NTP systematic review of the human, experimental animal, and mechanistic/*in vitro* literature

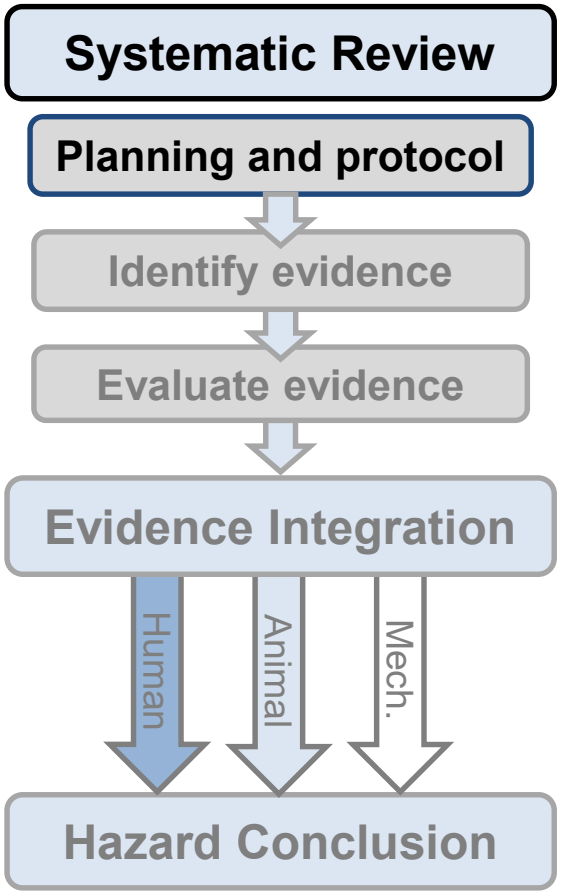
Objective
Determine whether fluoride exposure is associated with neurodevelopmental and cognitive effects in humans

NTP fluoride systematic review

Planning and protocol

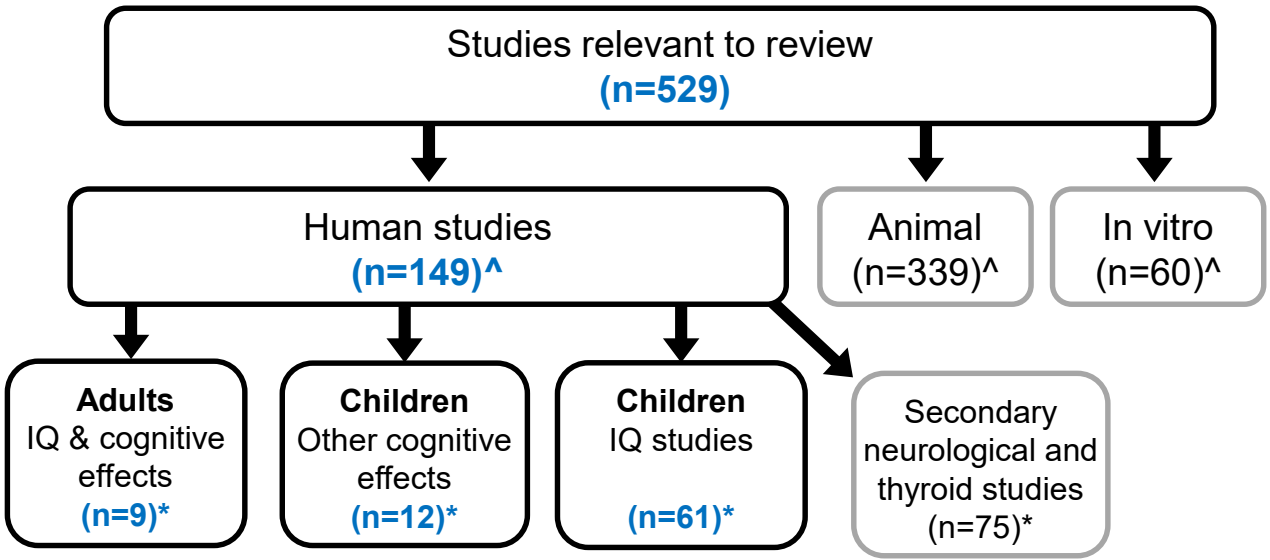
- Protocol posted to website in July 2017
  https://ntp.niehs.nih.gov/go/785076

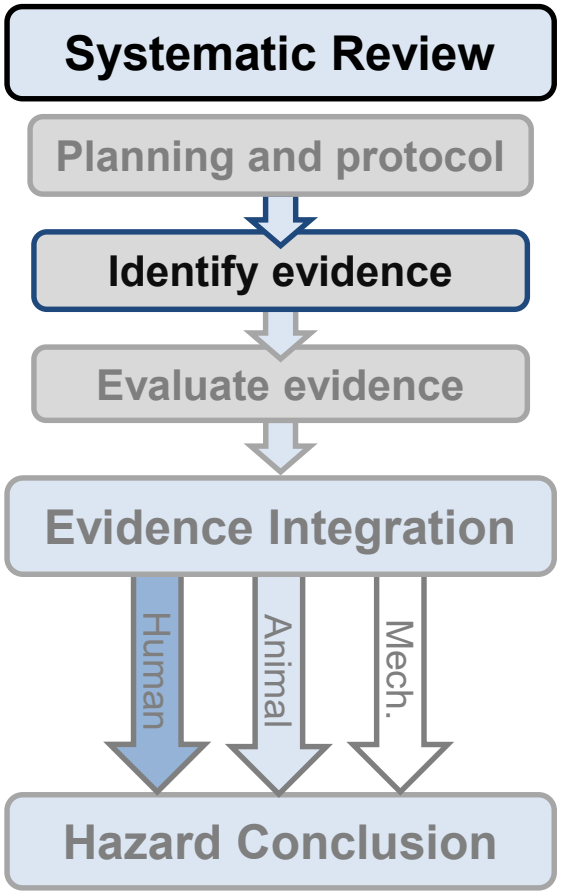




NTP fluoride systematic review

23,497 references screened

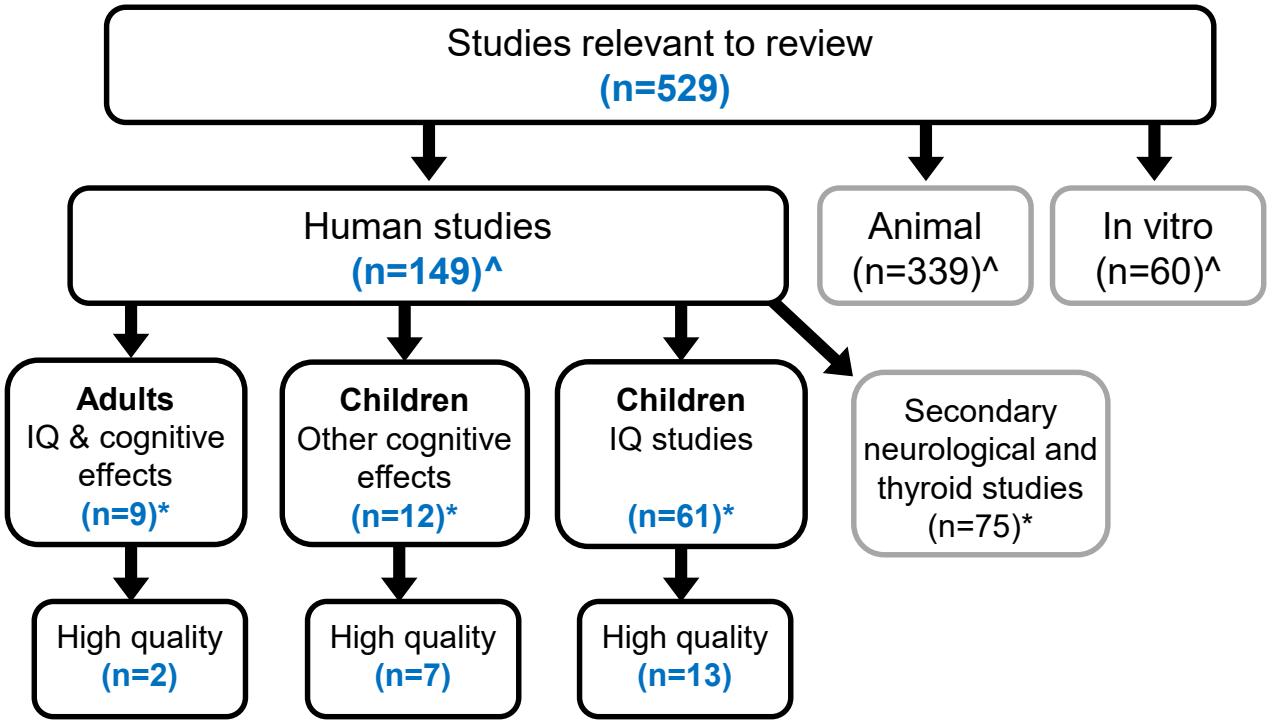


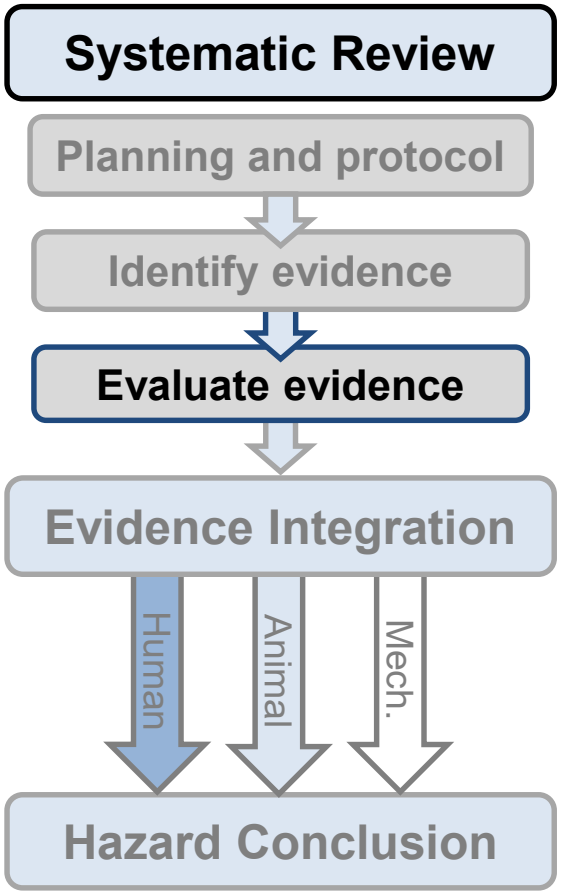


Note some studies addressed more than one evidence stream (^) or more than one type of outcome (*) so counts are not mutually exclusive

Risk of bias/study quality assessment

High quality=low risk of bias





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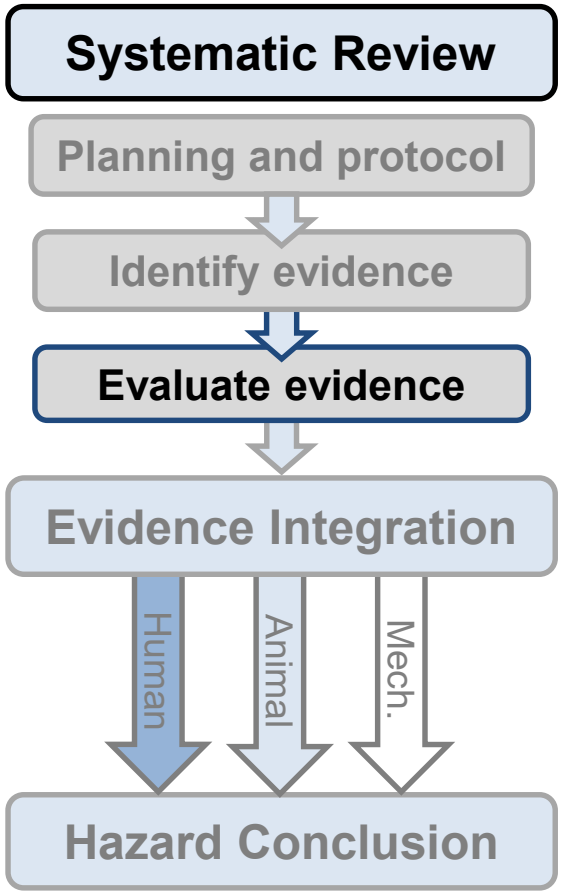
Risk of bias/study quality assessment*

Three key determinants

- Potential for confounding
- Exposure characterization
- Outcome assessment



*High quality=low risk of bias

Potential for confounding

- High quality studies of IQ and other cognitive effects in children with low potential bias due to confounding
  - Potential co-exposures and factors important for study population, outcome
- Confounding ruled out as major concern across studies
  - Results consistent despite variability in confounders considered, different populations

Key confounder

✓ Accounted for potential confounder

Potential confounding factors identified *a priori* and considered in studies of IQ and other cognitive effects in children (adapted from Figure 6 in document)

Study location	Subject characteristics				Other exposures					Socio-economic factors		Parental characteristics				Other
	Age	Sex	Race/ethnicity	Health factors	Arsenic	Smoking	Iodine	Lead	Other (in water)	S.E.S.	Caregiving environment (e.g., HOME score)	Demographics	Reproductive	Health factors	Parental IQ	Other
High quality studies rated "probably low" for risk of bias due to confounding																
Barberio 2017b (Canada)	✓	✓			✓			✓		✓						
Bashash 2017 (Mexico)	✓	✓			✓	✓		✓	✓	✓	✓	✓	✓		✓	✓
Bashash 2018 (Mexico)	✓	✓				✓		✓	✓	✓	✓	✓	✓			✓
Choi 2015 (China)	✓	✓		✓	✓			✓		✓		✓	✓	✓		✓
Cui 2018 (China)	✓	✓	✓	✓	✓											
Green 2019 (Canada)	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Rocha-Amador 2007 (Mexico)	✓			✓	✓			✓		✓						
Saxena 2012 (India)	✓	✓		✓	✓			✓		✓						✓
Seraj 2012 (Iran)	✓	✓					✓	✓		✓						✓
Xiang 2011 (China)	✓	✓					✓	✓		✓						
Yu 2018 (China)	✓	✓		✓	✓	✓	✓	✓	✓	✓			✓			✓
Zhang 2015b (China)	✓	✓			✓		✓	✓	✓	✓						✓

Fluoride exposure assessed with a variety of methods ranging from group-level to individual measures

- Comparison of two geographic areas with differing levels of fluoride exposure
  - High naturally occurring fluoride or artificially fluoridated areas vs. low or non-fluoridated areas
  - High levels of dental fluorosis vs. without
  - Burning fluoride-containing coal vs. not
- More confidence in comparison between groups if study reported individual measures to verify differences in exposure between groups
  - e.g., urine, serum, dental fluorosis in children

Individual measures of exposure considered more accurate than group-level measures

- Individual drinking water levels
- Estimates of fluoride intake
  - Captured by daily water consumption and drinking water levels, intake of other water-based beverages, green and black tea, consumption of tap vs. bottled water, etc.
- Urinary levels (e.g., maternal urinary fluoride) capture all ingested fluoride and considered valid measure of fluoride exposure
  - 24-hour urines, repeated spot samples throughout pregnancy, spot samples (shown to approximate a 24-hour urine sample when adjusted for dilution)
  - When comparing studies with different measures, useful to note that 1 mg/L of urinary fluoride roughly corresponds to 1 mg/L of fluoride in drinking water in fluoridated areas

13 high quality IQ studies in children

- Studies conducted in China, Mexico, Canada, India, and Iran
- All 13 studies report statistically significant ($p<0.05$) associations between fluoride exposure and decreased IQ
  - 2 recent North American prospective cohort studies (Mexico and Canada)
  - 11 cross-sectional studies: 9 considered functionally prospective in nature (i.e., exposure occurred prior to outcome)
- 41 of 48 lower quality studies of IQ in children provide consistent supporting evidence of association between fluoride exposure and decreased IQ
- 7 high quality studies describe associations between fluoride exposure and other measures of cognitive development
  - Hand-eye coordination, total neurobehavioral assessment, behavioral capacity, or learning disabilities

Recent North American prospective cohort studies

512 mother-child pairs from MIREC cohort in Canada (Green *et al.* 2019)

- Repeated urinary measures from each trimester of pregnancy
  - 1 mg/L increase of maternal urinary fluoride (MUF) associated with decrease of 4.6 IQ points in boys but not in girls
- Average fluoride intake over duration of pregnancy (n=400)
  - 1 mg/L increase of maternal fluoride intake associated with decrease of 3.7 IQ points in boys and girls

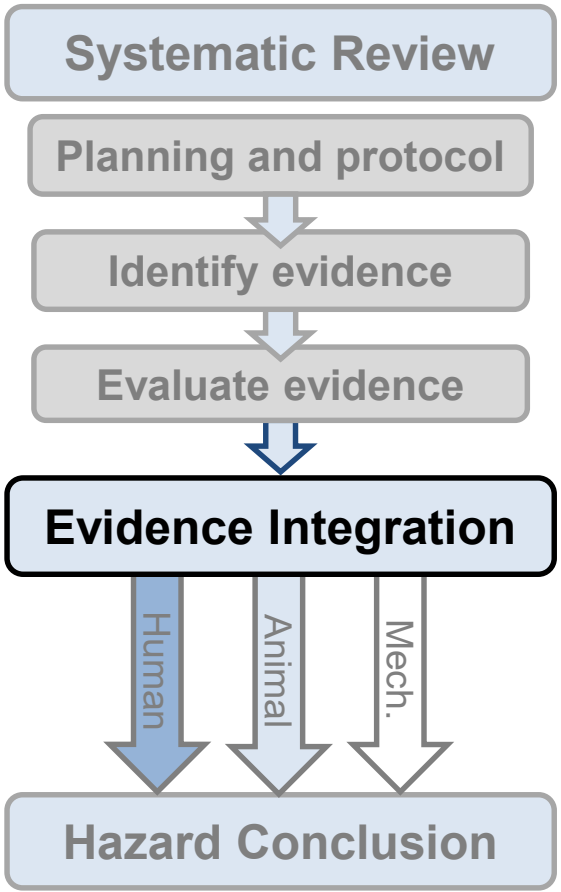
211 mother-child pairs from ELEMENT cohort in Mexico (Bashash *et al.* 2017)

- Repeated urinary measures throughout pregnancy
  - 0.5 mg/L increase of MUF associated with decrease of 2.5 IQ points, boys and girls analyzed together

Evidence integration

Develop level of evidence rating for each group of studies

- Four possible ratings: *high, moderate, low, inadequate*
- Represents confidence that studies reflect the true relationship between exposure and outcome
- Three groups of studies: children, adults, and animals



Level of evidence conclusion in children

Based on the high quality studies in children

Moderate level of evidence that high fluoride exposure is associated with decreased IQ and other cognitive effects in children

Summary of studies in adults

Limited number of high quality studies

- Two high quality cross-sectional studies
  - No consistent evidence of an association between cognitive impairment and exposure to fluoride
- Seven lower quality cross-sectional studies that provided some evidence of cognitive impairment in adults

Level of evidence conclusion in adults

Inadequate level of evidence that fluoride exposure is associated with cognitive effects in adults

Level of evidence conclusion in animals

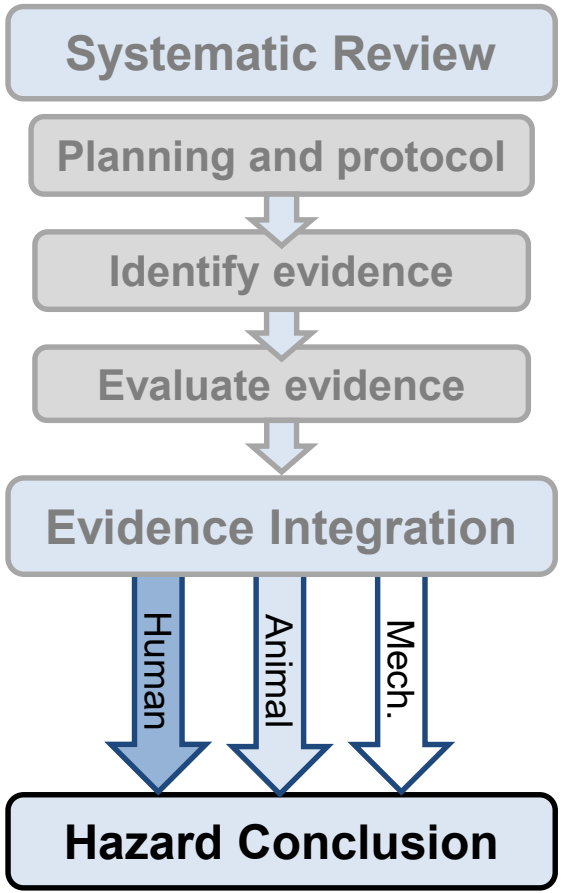
Inadequate level of evidence from animal studies

- Animal data considered *inadequate* to evaluate the effects of fluoride on IQ in humans
- Update to NTP's 2016 systematic review of experimental animal data
  - Low to moderate evidence that learning and memory is diminished in animals exposed to fluoride in diet or drinking water
  - Two main issues: (1) inability to distinguish effects of fluoride on motor and sensory functions from effects on learning and memory; (2) concerns for risk of bias (e.g., lack of randomization, blinding, etc.)
  - NTP conducted experimental animal studies to assess uncertainties, incorporated into this review
- There is evidence for effects of fluoride on neurodevelopment in animals but these do not contribute to evaluation of effects on IQ

Hazard conclusions

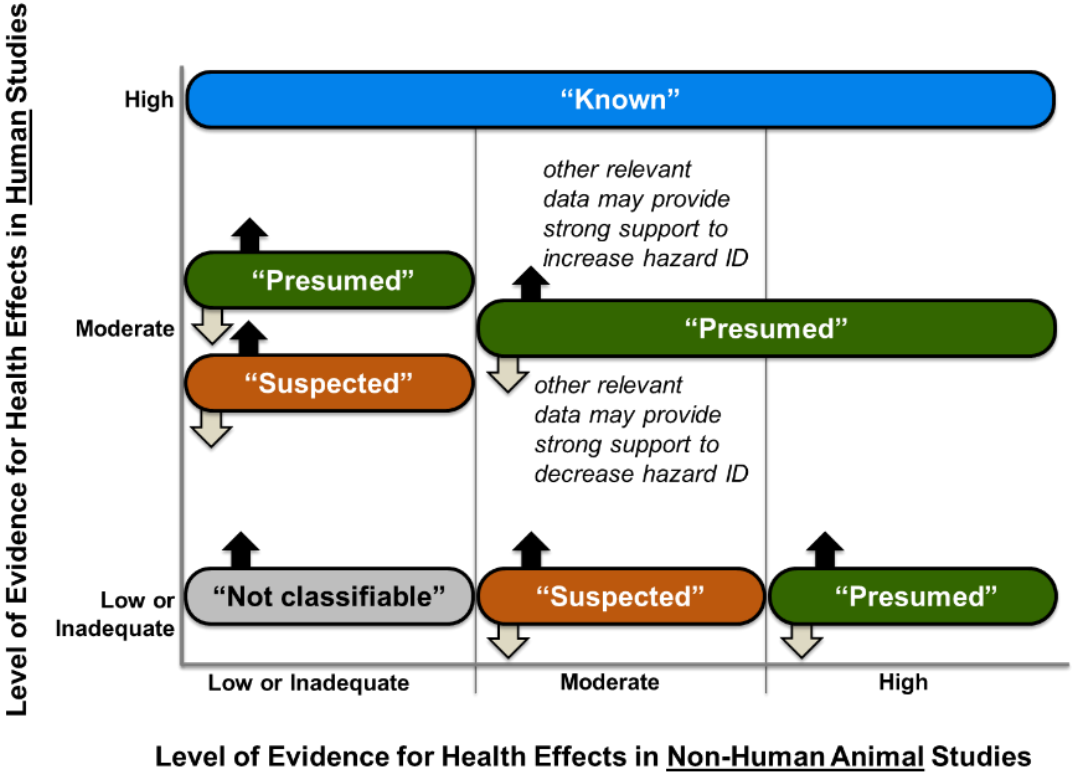
Conclusion on four-level scale

- Known
- Presumed
- Suspected
- Not classifiable



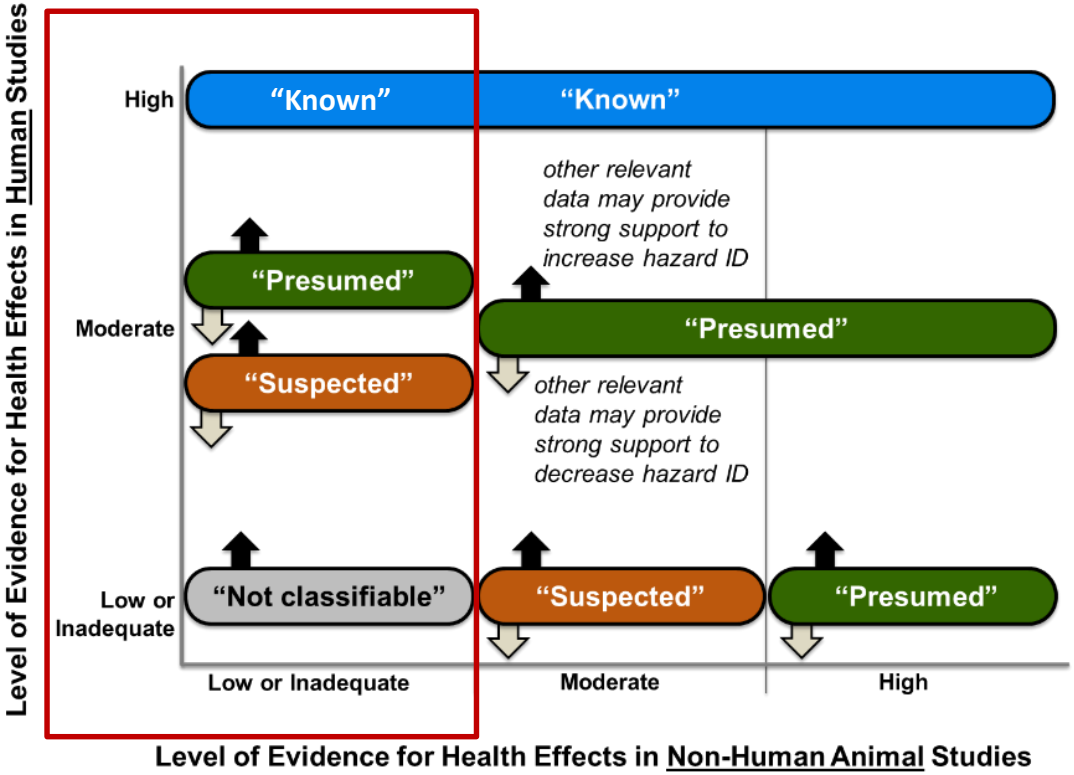
Developing hazard conclusions

Integrate evidence streams to develop hazard conclusion



Steps to integrate evidence

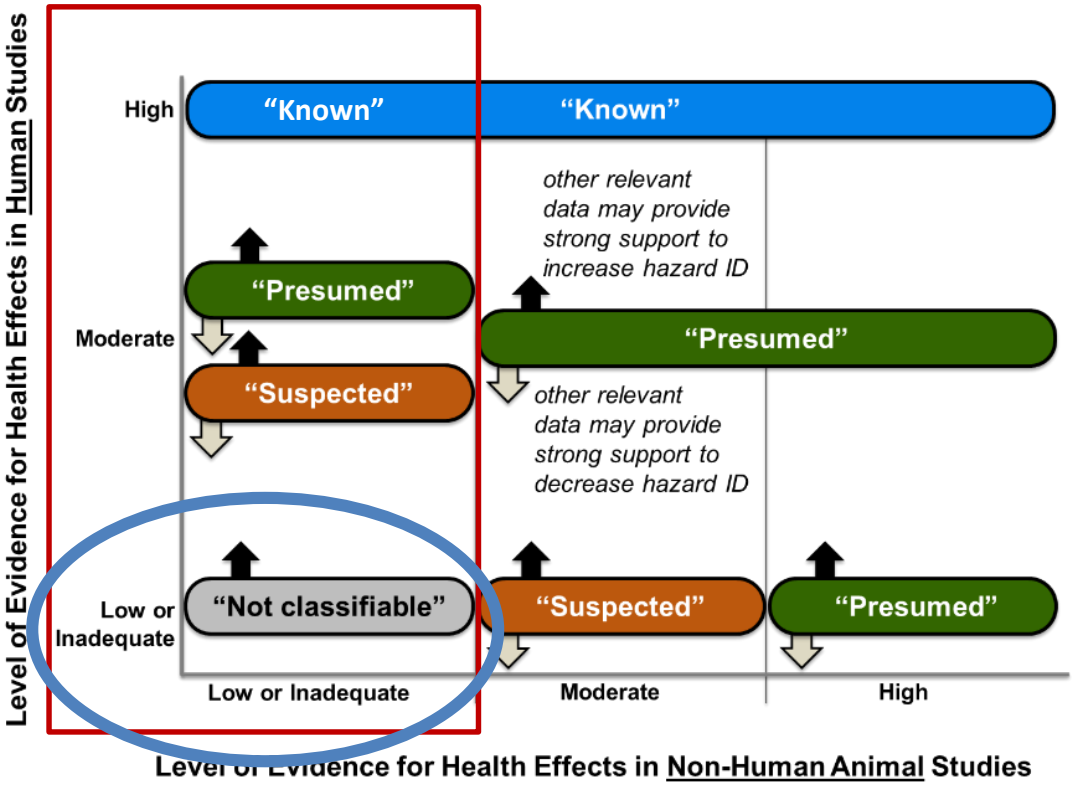
Conclusions based on human data given inadequate animal data



- Hazard conclusions developed for two bodies of evidence
  - Adults
  - Children

Developing hazard conclusion in adults

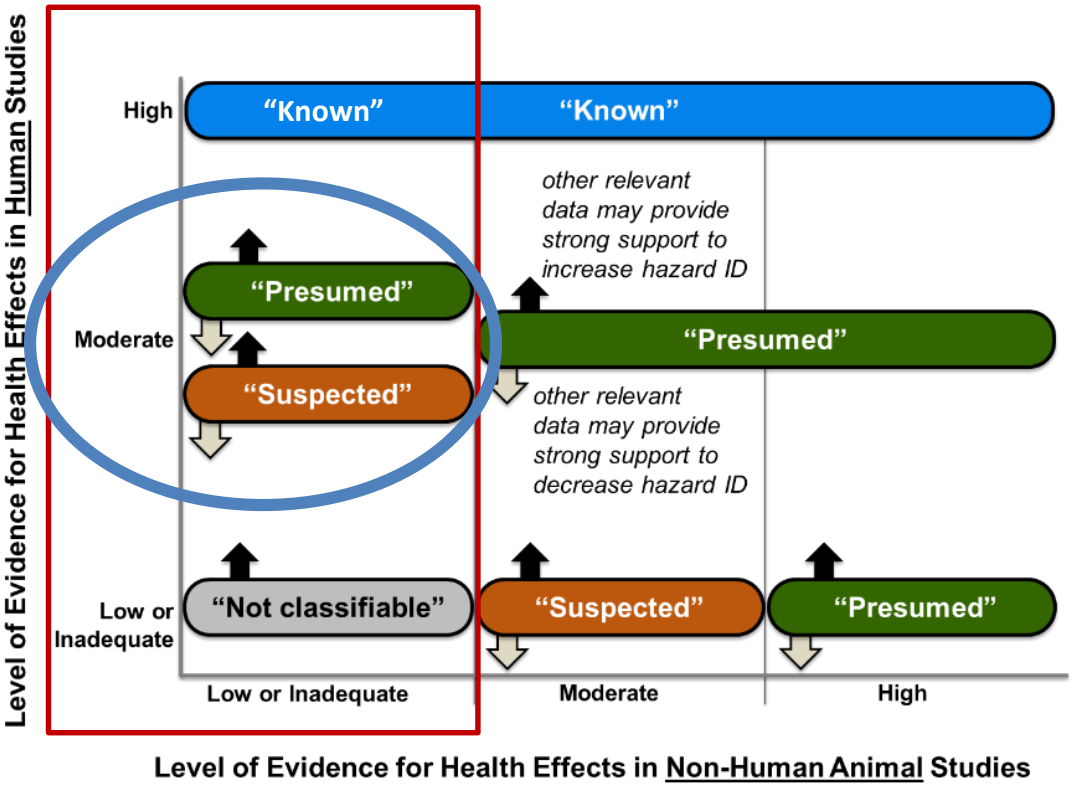
Conclusions based on human data given inadequate animal data



- Human body of evidence from studies in adults considered
  - ***inadequate level of evidence***

Developing hazard conclusion in children

Conclusions based on human data given inadequate animal data



- Human body of evidence from studies in children considered
  - ***moderate level of evidence***

Distinction based on:

- Robustness of body of evidence
- Potential impact of additional studies

Level of evidence and hazard conclusions

Studies in children

Level of evidence

High (++++) The true effect is highly likely to be reflected in the apparent relationship.

Moderate (+++) The true effect is likely to be reflected in the apparent relationship, but there is a possibility that it is substantially different.

Low (++) or **Very Low** (+) The true effect may be (low) or is likely (very low) different from the apparent relationship.

And further research...

Is very unlikely to decrease confidence in the association → **Presumed**

Is likely to change the confidence in the association → **Suspected**

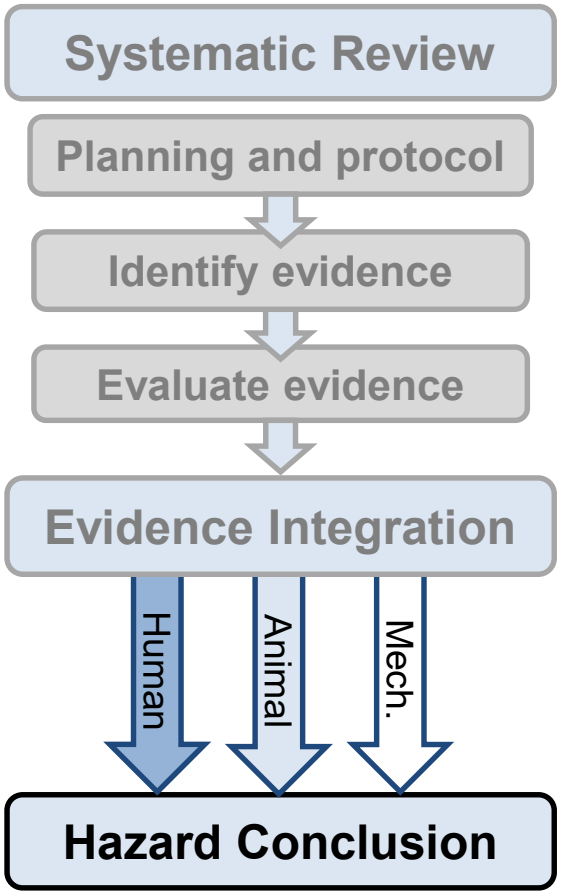
Factors considered

- Magnitude of effect
- Size of the study populations
- Whether there were multiple populations examined
- Consistency across studies

Hazard conclusions

Four level scale: known, presumed, suspected, and not classifiable

- Exposure to fluoride exposure is ***presumed*** to be a cognitive neurodevelopmental hazard to children
- Exposure to fluoride is ***not classifiable*** as a cognitive hazard to adults



NTP draft conclusion on neurodevelopmental effects in children

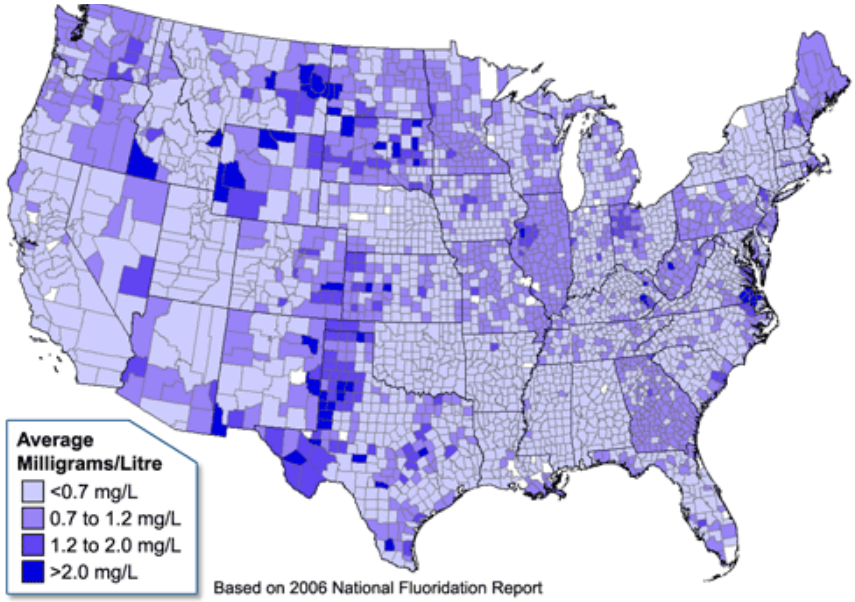
Presumed conclusion based on extent, consistency and magnitude of effect in children across multiple populations (Canada, Mexico, China, India and Iran)

- 13 high quality studies reported association between high fluoride exposure and decreased IQ in children
  - Two North American prospective cohort studies with repeated maternal urinary fluoride measures and relatively large magnitudes of effect (3-5 IQ points)
  - 11 cross-sectional studies (9 of which functionally prospective in nature), also showed consistent pattern of evidence
- Supported by consistency of lower quality studies (41 of 48 reported an association between fluoride exposure and decreased IQ)
- Therefore, any new study (even if negative) is unlikely to decrease the hazard conclusion

Context on fluoride exposure in the United States

- 75% of U.S. population served by artificially fluoridated water systems
- In 2015 U.S. Public Health Service lowered recommended optimum level of fluoride in water from 0.8-1.2 mg/L to 0.7 mg/L
  - Due to increasing dental fluorosis in children
- Cross-section of fluoride in drinking water in the United States estimated from 2013-2014 NHANES data ranges from 0.03-1.5 milligrams/liter (mg/L) (Jain *et al.* 2017)
- Fluoridated drinking water provides 30-70% of typical individual's total exposure
- Other sources include dental products, green and black tea, foods and beverages

Average Fluoridation Levels by County (naturally occurring and added)



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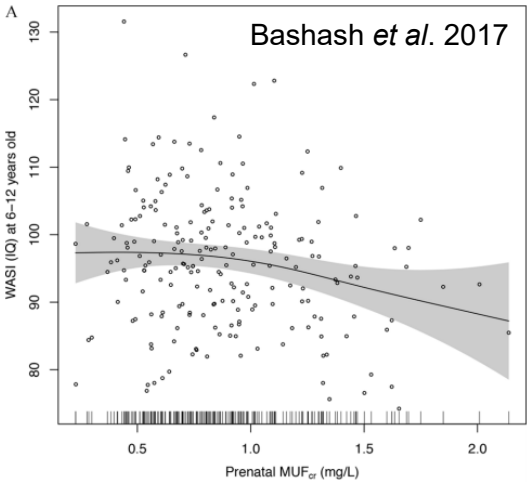
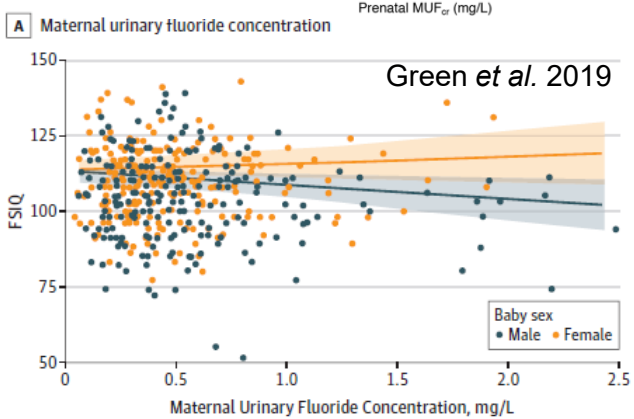
Relevance to the United States

Generalizing results from IQ studies to U.S. population is difficult

- Many studies conducted in areas with higher fluoride drinking water levels than in the United States (>1.5mg/L*)
- 31 studies compared a reference/low exposure group to higher exposure group
  - Of these, 8 had an exposed group <1.5 mg/L (two of these were high quality)
- Several studies provided information to evaluate dose-response in lower exposure range
- However, results inconsistent, unclear if IQ changes in children occur at lower fluoride levels





*Range of 0.03-1.5mg/L fluoride in U.S. drinking water from NHANES (Jain 2017)

Challenges and limitations of the database

- No studies conducted in the United States
- Few studies in children from communities served by optimally (<0.7mg/L) fluoridated vs. non-fluoridated water systems
- Few studies of neurobehavioral effects in adults or attention-related disorders in children
- Most studies did not stratify by gender

Thank you! Questions?