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# **NTP Evaluation of Fluoride Exposure and Potential for Developmental Neurobehavioral Effects**

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# Program of Activities

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- Sources and extent of exposure
- Prior literature reviews of human and animal evidence for neurological effects
- NTP Laboratory studies to address already identified key data gaps in animal literature
- Proposed systematic review
  - Will be timed to incorporate results from NTP laboratory studies



# Sources of Exposure

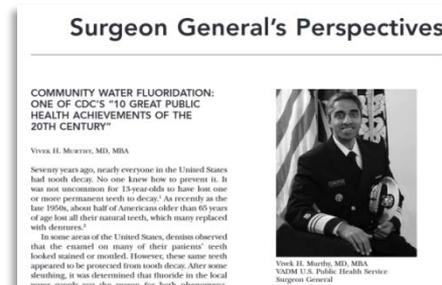
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- Drinking water is main source of exposure
- Other sources include foods, beverages, dental products (toothpaste, mouth rinses), supplements, industrial emissions, pharmaceuticals, and pesticides (e.g., cryolite and sulfuric fluoride)
- Soil ingestion can be a source of exposure in young children

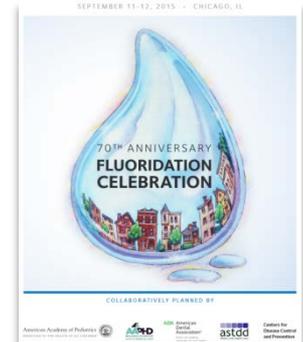


# Fluoride to Prevent Tooth Decay

- Fluoride helps prevent dental caries through topical remineralization of tooth surfaces
  - Community water, toothpaste, mouth rinses, gels
- Community water fluoridation began in 1945
  - 67% of US population (200 million people, 12,341 water systems)
  - Practiced in ~25 countries (can be provided through other vehicles such as salt)
- Water fluoridation program considered one of the most significant public health achievements of the 20<sup>th</sup> century



PUBLIC HEALTH REPORTS, JULY-AUGUST 2015





# Guidance on Community Water Fluoridation

- Updated 2015 US Public Health Service (PHS) recommendation is 0.7 mg/L\*
  - Provides best balance for protection of dental caries while limiting risk of dental fluorosis (staining or mottling of teeth)
  - Not regulatory, decisions made at state and local levels
- US EPA current enforceable standard for drinking water is 4.0 mg/L to protect against severe skeletal fluorosis
  - EPA in process of reviewing maximum allowable amount

\*U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. 2015. PHS Recommendation for Fluoride Concentration in Drinking Water.

[http://www.publichealthreports.org/documents/PHS\\_2015\\_Fluoride\\_Guidelines.pdf](http://www.publichealthreports.org/documents/PHS_2015_Fluoride_Guidelines.pdf)



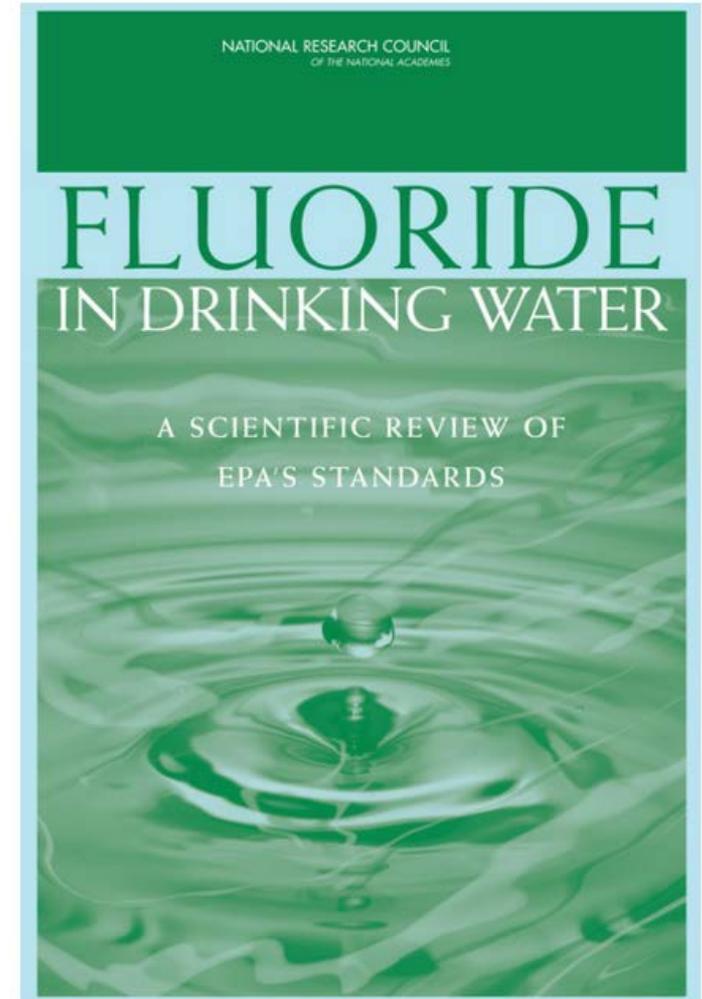
# Concerns for Potential Fluoride Toxicity

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- Most concerns in areas of bone fractures and dental/skeletal fluorosis, lowering of IQ, cancer, and endocrine disruption
  - Best document and established consequences are dental fluorosis, skeletal fluorosis, and increased risk of bone fractures (EPA 2010)
    - Dental fluorosis considered in 2015 PHS recommendation, EPA current standard based on skeletal fluorosis
  - Associations with lower IQ, cancer, and endocrine disruption are more controversial
- In addition to developmental neurobehavioral outcomes, NTP has received nominations to do literature-based analyses for cancer and endocrine disruption



- **Charge:** Evaluate whether EPA's maximum contaminant level goal (MCLG) of 4 mg/L and secondary maximum contaminant level (SMCL) of 2 mg/L in drinking water are adequate to protect health





# 2006 NRC Report: Overall Conclusion

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- MCLG of 4 mg/L for fluoride should be lowered.  
“Exposure at the MCLG clearly puts children at risk of developing severe enamel fluorosis”



## Epidemiology studies and IQ

- A few studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water
- Studies lacked sufficient detail for full assessment of quality and relevance to U.S. population
- Results appear significant enough to warrant additional research on the effects of fluoride on intelligence



## Animal studies and neurological outcomes

- A few animal studies reported alterations in the behavior of rodents, but changes not considered substantial in magnitude
- More compelling were studies on molecular, cellular, and anatomical changes in the nervous system
  - Suggest functional changes could occur
- More research is needed to clarify the effect of fluoride on brain chemistry and function



# Recent Systematic Review of Human Evidence

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- 2015 Systematic review conducted for the Republic of Ireland's Department of Health by the Health Research Board
- For fluoride-endemic areas, “studies suggest, but do not prove,” that high levels of naturally occurring fluoride in water ( $\geq 1.5$  mg/L) may be associated with lowering of IQ
  - Concerns for study quality raised, especially lack of accounting for other factors that could impact IQ (nutritional status, socioeconomic status, iodine deficiency/excess, mineral and other chemicals in water associated with neurotoxicity)
  - Conclusions consistent with 2012 meta-analysis (Choi et al.)
- No evidence of an association with lowered IQ in a prospective cohort study in New Zealand evaluating community water fluoridation (Broadbent et al. 2015)



# Draft NTP Systematic Review of Animal Studies

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- Conducted in collaboration with Australian National Health and Medical Research Council (NHMRC) to illustrate application of OHAT systematic review methodology for animal data
- Undergoing external peer-review, expected to be finalized and published in 2016
- Considered exposure during development or adulthood
- Identified studies on a broad range of neurobehavioral outcomes



# Draft NTP Systematic Review of Animal Studies

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- ~5,000 studies screened, 61 included of which 44 included assessment of learning and memory
  - 40+ studies published since 2006 NRC report
  - Most studies were relatively high dose (>5 mg/L)
- Found evidence of potential detrimental effects on learning and memory in rats and mice
  - Confidence lowered due to limitations in study design/analysis and poor reporting quality, e.g., randomization, blinding, control for litter effects, purity and source of fluoride
  - Concern for potential confounding by other deficits in performance, e.g., motor function or fear responses
  - Very few studies addressed developmental effects at low concentrations of fluoride (3 studies tested concentrations  $\leq 10$  mg/L)



# Proposed NTP Laboratory Animal Studies

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- Lead by Dr. Jean Harry, Group Leader for NTP Laboratory Neurotoxicology Group
- Focused on assessing learning and memory in rats following developmental exposure
  - Address study design limitations and potential confounding
- Study is in early planning stages
  - Will conduct pilot studies to confirm previous findings
  - If justified, follow-up studies would address potential effects using dose levels more comparable to concentrations recommended for water fluoridation (currently 0.7 mg/L, historically 0.8-1.2 mg/L)



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# **Proposed Systematic Review on Fluoride and Developmental Neurobehavioral Outcomes**



# Nomination History

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- Nominated by private individuals on June 8, 2015
  - Federal Register Notice (October 7, 2015, comment period ended November 6)
    - 2 comments received (provided list of studies to consider, supported evaluation)



## Objective

- Undertake a systematic review of the human, animal, and mechanistic studies to develop hazard identification conclusions about whether fluoride is a developmental neurobehavioral toxicant
  - Examples of data collected to assess biological plausibility: brain-related molecular, cellular, morphometric or histological endpoints; thyroid hormone-related measures
- Learning and memory behavior is primary focus, but other behaviors will be included, e.g., motor function/fear to assess potential confounding



## Approach for systematic review

1. Find relevant studies
  - Human, experimental animal, and in vitro
2. Extract data from relevant studies
3. Assess the internal validity (risk of bias) of individual studies
4. Summarize the evidence



# Proposed Literature-based Analysis

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## Approach for systematic review

5. Synthesize the evidence
  - Conduct meta-analyses, if appropriate, and sensitivity analyses
6. Rate confidence in the body of evidence
7. Translate confidence ratings into level of evidence of health effects
8. Combine the level of evidence ratings for human and animal data and consider the degree of support from mechanistic data
9. Describe findings in the context of human exposure levels; describe limitations of the evidence base and systematic review; identify research needs



PECO Element	Evidence
Population	<ul style="list-style-type: none"><li>• Humans</li><li>• Experimental animal models (non-human mammalian)</li><li>• in vitro models</li></ul>
Exposure	<ul style="list-style-type: none"><li>• Sodium fluoride (7681-49-4), fluorosilicic acid (16961-83-4), sodium fluorosilicate (16893-85-9), soluble fluorine (7782-41-4) OR other forms that readily dissociate into free fluoride ions (e.g., potassium fluoride, calcium fluoride, ammonium fluoride)</li><li>• Exposure in humans or animals during development</li></ul>
Comparators	<ul style="list-style-type: none"><li>• Observational: a comparison population exposed to lower levels</li><li>• Experimental: vehicle-only treatment controls</li></ul>
Outcomes	<ul style="list-style-type: none"><li>• <i>Primary outcomes:</i> Learning and memory-related outcomes</li><li>• <i>Secondary outcomes:</i> Other types of neurobehavioral response (e.g., motor/fear), brain-related molecular, cellular, morphometric or histological endpoints; thyroid hormone-related measures</li></ul>



# Protocol & Draft Report Development

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- Concept document intended to solicit feedback on proposed question to be addressed
  - Public comment period ends January 8, 2016
- Protocol is detailed methods document prepared after end of public comment period on concept
  - Protocol based on guidance outlined in 2015 OHAT Handbook “Systematic Review and Evidence Integration”
  - Protocol will be posted on OHAT website
- Topic-specific experts are used to review and implement protocol, e.g., experts in fluoride, epidemiology, toxicology, neurobehavior, systematic review and evidence integration
- Draft NTP evaluation is peer-reviewed in public session with opportunity for written and oral public comments



# Next Steps and Timeline

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- Present draft concept at December 1-2 NTP BSC meeting
- Spring 2016:
  - Post protocol on OHAT website
  - Release NTP report on existing animal studies
  - Scoping review activities on endocrine and cancer nominations
- Anticipate draft systematic review for public comment and peer review in 2018



# Review Questions

1. Please comment on the clarity and validity of the rationale for the proposed evaluation as articulated in the draft concept.
2. Please comment on the merit of the proposed evaluation relative to the goals of the NTP.  
*The NTP's objectives are to: provide information on potentially hazardous substances; develop and validate improved test methods; strengthen the science base in toxicology; coordinate toxicology testing programs across DHHS.*
3. Please comment on the proposed approach for the evaluation.
4. Please comment on the scope of the proposed evaluation and its appropriateness, relative to the public health importance of the issue.
5. What priority (low, moderate, or high) should NTP give the proposed evaluation given the rationale, merit, and scope?
6. Prove any other comments you feel staff should consider in developing this evaluation.