NTP
National Toxicology Program

NTP Board of Scientific Counselors (BSC) Working Group Report

on the

Draft State of the Science Monograph and the Draft Meta-Analysis Manuscript on Fluoride

David L. Eaton, PhD, DABT, FATS
BSC Working Group Chair

NTP Board of Scientific Counselors Meeting
May 4, 2023

Agenda

- Background
- BSC WG
- BSC WG's Assessment
- BSC WG Report
- Summary

- Key:
  - BSC = Board of Scientific Counselors
  - DTT = Division of Translational Toxicology
  - HHS = Department of Health and Human Services
  - NASEM = National Academies of Science, Engineering, and Medicine
  - SoS = State of the Science
  - M-A = Meta-analysis
  - WG = Working Group

Background

In 2016, NTP initiated a systematic review to evaluate the scientific evidence for neurobehavioral health effects from exposure to fluoride during development (*NTP Monograph on Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*)

Date	NTP Monograph on Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects
September 2019 – March 2020	NASEM peer review of **Draft NTP Monograph (September 6, 2019),** a systematic review of the literature with proposed hazard classification that fluoride is presumed to be a cognitive neurodevelopmental hazard to humans
March 2020 – September 2020	NTP addressed NASEM Report 1 comments, added a meta-analysis as proposed by NASEM, and prepared the **Revised Draft NTP Monograph**
September 2020 – February 2021	NASEM peer review of **Revised Draft NTP Monograph (September 16, 2020)**
February 2021 – July 2021	NTP addressed NASEM Report 2 comments, removed the hazard classification for fluoride, and split the monograph into two documents: **(1) State of the Science Monograph** and **(2) Meta-Analysis Manuscript**

Date	State of the Science Monograph
July 2021 – June 2022	HHS units reviewed and offered comments
November 2021 – February 2022	External peer review by five experts
September 2022	Draft State of the Science Monograph, reflects comments received

Date	Meta-Analysis Manuscript
July 2021 – June 2022	HHS units reviewed and offered comments
July 2022	Draft Meta-Analysis Manuscript and Draft Meta-Analysis Manuscript – Supplemental Materials, reflects comments received

HHS = Department of Health and Human Services
NASEM = National Academies of Science, Engineering, and Medicine

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Background

NTP Director and NTP BSC Chair jointly decided to convene a BSC WG

- The BSC Working Group's task would focus on the review and assessment of NTP authors' responses to comments on the Draft *State of the Science Monograph* and Draft *Meta-Analysis Manuscript*
- The BSC WG would access:
  - External peer-review and/or federal agency comments on the two documents
  - Draft SoS Monograph (Sept 2022) and Draft M-A Manuscript (Jul 2022) (which reflect comments received)
- As background, the BSC WG would also have access to:
  - Revised Draft NTP monograph that went to NASEM (Sept 16, 2020) AND
  - NTP authors' responses to the NASEM committee's review of the Revised Draft NTP Monograph (Sept 16, 2020)
  - Oct 2021 and May 2022 "intermediate" versions of the Draft SoS Monograph

Charge:

To evaluate the adequacy of NTP* responses to external peer review and/or federal agency comments received during the development of the *Draft State of the Science Monograph* and the *Draft Meta-Analysis Manuscript*

- BSC Working Group will <u>not</u> provide independent peer review of the *State of the Science Monograph* or *Meta-Analysis Manuscript*
- BSC Working Group <u>may offer</u> perspectives and suggest revisions that might improve the quality of either document

*Staff within the Division of Translational Toxicology, National Institute of Environmental Health Sciences developed the Draft SoS Monograph and the Draft M-A Manuscript on behalf of the NTP

WG Selection and Membership

- Dr. Woychik asked David Eaton, PhD, then Chair of the BSC, to form the WG (Feb 2022)
- Dr. Eaton decided that WG should consist of no more than10 members, including chair, with diverse and appropriate scientific expertise
  - Analytical chemistry, pre- and perinatal and early childhood neurodevelopment, environmental epidemiology, exposure assessment, trace element toxicology, meta-analysis, neonatology, neurodevelopmental toxicology, occupational epidemiology, pediatric dentistry, pediatrics, psychology, public health, risk assessment, statistical methods, systematic review, mechanistic studies and toxicology
- Dr. Eaton identified potential WG members with appropriate scientific expertise, with consideration of nominations from HHS units
  - Potential WG members were screened for COI
  - Drs. Eaton and Wolfe interviewed each candidate
- Dr. Eaton made final selection of individuals to serve on the BSC WG

BSC WG Roster

David L. Eaton, PhD (Chair)
Emeritus Professor, University of Washington
Adjunct Professor of Pharmacology and Toxicology
University of Arizona

Antonia M. Calafat, PhD
Chief, Organic Analytical Toxicology Branch
Division of Laboratory Sciences
National Center for Environmental Health
Centers for Disease Control and Prevention

Pamela Den Besten, DDS, MS
Professor of Orofacial Sciences, School of Dentistry
University of California, San Francisco

Stephanie M. Engel, PhD
Professor, Department of Epidemiology
Director, Center for Early Life Exposures and Neurotoxicity
Gillings School of Global Public Health
University of North Carolina Chapel Hill

Michael K. Georgieff, MD
Executive Vice Chair and Martin Lenz Harrison Land Grant Professor, Department of Pediatrics
Director, Center for Neurobehavioral Development
University of Minnesota Medical School

Matthew J. Maenner, PhD
Chief, Child Development and Disability Branch
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

David Michaels, PhD, MPH
Professor, Department of Environmental and Occupational Health
The Milken School of Public Health, George Washington University

Sally C. Morton, PhD, MSc
Executive Vice President, Knowledge Enterprise
Professor, College of Health Solutions and School of Mathematical & Statistical Sciences, Arizona State University

Sharon K. Sagiv, PhD, MPH
Associate Adjunct Professor, Division of Epidemiology and Biostatistics
Investigator, Center for Environmental Research and Children's Health
School of Public Health, University of California, Berkeley

Ian Saldanha, MBBS, MPH, PhD
Associate Professor, Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Adjunct Associate Professor, Department of Health Services, Policy and Practice
Brown University School of Public Health

Questions?

Review comment sets were provided to WG for evaluation

- Comments on Draft SoS Monograph and Draft M-A Manuscript
  - 13 sets of reviewer comments (325 comments) with NTP authors' responses on the Draft SoS Monograph
  - 9 sets of reviewer comments (141 comments) with NTP authors' responses on the Draft M-A Manuscript
  - All reviewer comments were anonymized as to the reviewer's identity

Comment Sets

- Comment sets coded and anonymized to source
  - **SoS Monograph** comments coded by **Letter.Number**
  - **M-A Manuscript** comments coded by **Number.Letter**
  - Source of comments redacted

B2.13: ***Discussion page 78:*** *"Associations between lower total fluoride exposure [e.g., represented by populations whose total fluoride exposure was lower than the WHO Guidelines for Drinking- water Quality of 1.5 mg/L of fluoride (WHO 2017)] and children's IQ remain unclear."*

[redacted] **comment:** This language was commented on earlier. How is exposure in water correlated with overall exposure in this sentence?

Response: No change requested

- The statement relies on empirical observations of a close correspondence between drinking water concentrations and urinary fluoride concentrations first described prior to significant additional fluoride exposures from other sources such as dental products (see Kumar et al. (2017) [DOI 10.1007/s13201-016-0492-2] as an example). Our assessment of confidence in the association between higher fluoride exposure and lower children's IQ is supported by studies that report total fluoride exposures as represented by urinary measurements.

BSC WG Assessment:

The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

5.B: Issue: Limitations section

In its response letter, NASEM requested adding clarifying information in the manuscript. NTP itemized items in the state-of-the-science manuscript on limitations of the evidence based and the systematic review. However, these limitations do not address the following issues comprehensively:

Note: [redacted] comments on the protocol and literature search (numbered as "1" and "2" in the original comments) for the prepublication 2022 NTP Monograph are not reproduced here as they are not directly relevant to the meta-analysis. To avoid confusion, the number "3" was removed from following comment. See DocA1_Monograph for the monograph-relevant comments and responses.

BSC WG Assessment:

The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

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- Comment sets coded and anonymized to source
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5.B: Issue: Limitations section

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BSC WG Assessment:

The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

Comment Evaluation Process

- BSC WG met frequently, via Zoom, October 2022 – March 2023
  - Comment files, Draft SoS Monograph (Sept 2022), Draft M-A Manuscript (July 2022), and other background documents were posted to a secure website
  - Each comment was assigned by Dr. Eaton to an "evaluator pair" based on the nature of the reviewer's comment and BSC WG members' scientific expertise
  - BSC WG evaluator pairs reviewed each comment and assessed the adequacy of the NTP authors' response
    - If one or more members of an evaluator pair deemed a response "inadequate," the comment was discussed at a meeting with opportunity for input by other BSC WG members
    - BSC WG members reviewed draft final assessments and agreed to revisions to facilitate internal consistency across the Draft SoS Monograph and Draft M-A Manuscript
  - BSC WG's assessment compiled into a report

Assessment Categories

- Overall assessment of each reviewer's comment/NTP authors' response used one of the following three statements for both the Draft SoS Monograph and Draft M-A Manuscript:

  1. The BSC WG considers the NTP authors' response to the reviewer's comment adequate

*The statement would fill-in with either SoS Monograph or M-A Manuscript

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  1. The BSC WG considers the NTP authors' response to the reviewer's comment adequate
  2. The BSC WG considers the NTP authors' response to the reviewer's comment adequate but makes the following suggestion(s) to enhance the "SoS Monograph/M-A Manuscript"*
     - The BSC WG suggests …

*The statement would fill-in with either SoS Monograph or M-A Manuscript

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2. The BSC WG considers the NTP authors' response to the reviewer's comment adequate but makes the following suggestion(s) to enhance the "SoS Monograph/M-A Manuscript"*
   - The BSC WG suggests …
3. The BSC WG considers the NTP authors' response to the reviewer's comment inadequate
   - The BSC WG recommends …

[Note: These recommendations include revising the text, and/or providing additional information to better address reviewers' comments and/or improve the "SoS Monograph/M-A Manuscript"*]

*The statement would fill-in with either SoS Monograph or M-A Manuscript

Report's Organization:

- Chapter 1: Introduction and Summary of Assessment
- Chapter 2: SoS Monograph
- Chapter 3: M-A Manuscript
- Appendices (show track-change edits and/or embed reviewers' comments and NTP authors' responses)
  - Appendix I: NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review (September 2022 version)
  - Appendix II: Association Between Fluoride Exposure and Children's Intelligence: A Systematic Review and Meta-Analysis (July 2022 version)
  - Appendix III: BSC Working Group Members' Bibliographies

Presentation of Comments and Assessments

- Comments in BSC WG report are presented in standard format:
  - Numbering system is maintained
    - **SoS Monograph** comments coded by **Letter.Number**
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  - Redaction to source of comment

B2.13: ***Discussion page 78:*** *"Associations between lower total fluoride exposure [e.g., represented by populations whose total fluoride exposure was lower than the WHO Guidelines for Drinking- water Quality of 1.5 mg/L of fluoride (WHO 2017)] and children's IQ remain unclear."*

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BSC WG Assessment:

The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

5.K:

g. Provide the rationale for selecting individual outcomes from a single study when multiple outcomes were present

Response: Agree (change made)

- We reviewed the analyses to ensure that a consistent approach matching the data criteria outlined in the meta-analysis protocol was applied to all studies. Results were selected considering the most appropriate exposure metric, exposure range, exposure period, number of subjects, and statistical adjustment for potential confounders. See excerpt of eTable 2 referenced in our response to comment "a" above for study-specific effect estimates used in the meta-analysis.

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  - Redaction to source of comment
  - Comments' text **BLACK**
  - NTP authors' response **BLUE**
  - BSC WG's assessment **ORANGE**

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  - Comments' text **BLACK**
  - NTP authors' response **BLUE**
  - BSC WG's assessment **ORANGE**
    - Follow the rating scheme for responses:
      1. Adequate
      2. Adequate but AND BSC WG makes suggestion(s) …
      3. Inadequate AND the BSC WG recommends …

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1. **BSC WG Assessment**:

   The BSC WG considers the NTP authors' response to the reviewer's comment adequate.

2. **BSC WG Assessment**:

   The BSC WG considers the NTP authors' response to the reviewer's comment adequate but makes the following suggestion(s) to enhance the draft SoS Monograph:

   The BSC WG suggests that text within the draft SoS Monograph refer to Appendix E for information about the risk-of-bias assessment of the studies to increase clarity.

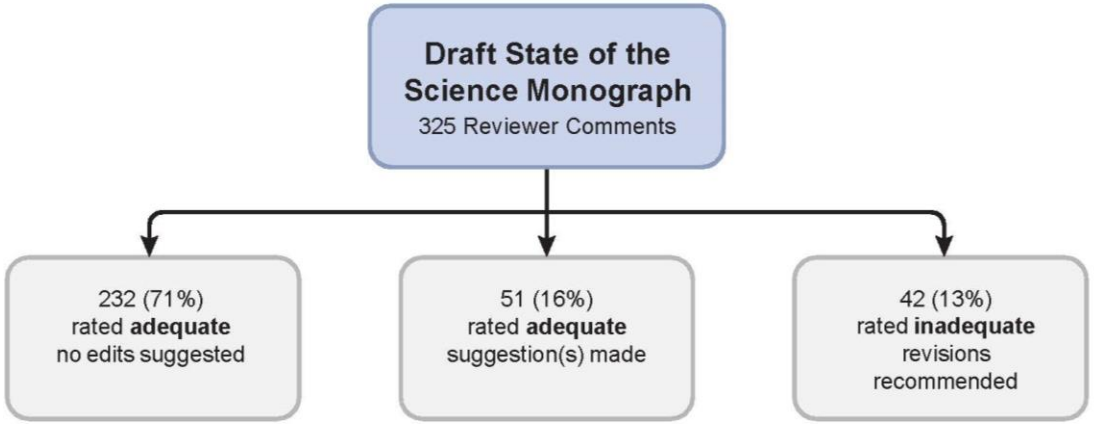
3. **BSC WG Assessment:**

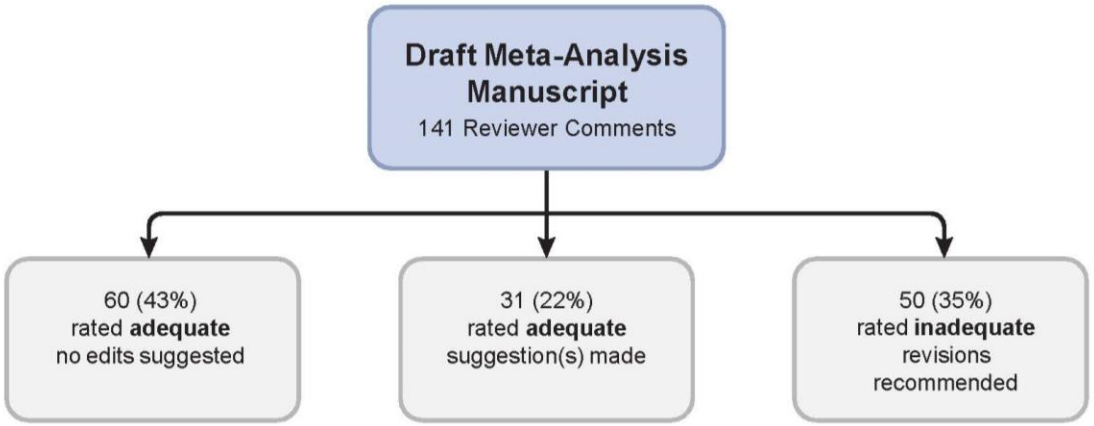
   The BSC WG considers the NTP authors' response to the reviewer's comment inadequate.

   The BSC WG agrees with the reviewer's comment and recommends that the authors include information in the Methods section of the draft SoS Monograph about how "well-established" analytical methods for measuring fluoride are defined rather than referring to the protocol or an appendix to the draft SoS Monograph.

Assessment Summary

- Draft SoS Monograph (325 comments from 13 different comment sets):
  - **87%** of the NTP authors' responses to reviewer comments were rated **adequate** and suggestions were provided to enhance the draft monograph when applicable
  - **13%** of the NTP authors' responses to reviewer comments were rated **inadequate** and recommended revisions were provided
- Draft M-A Manuscript (141 comments from 9 different comment sets):
  - **65%** of the NTP authors' responses to reviewer comments were rated as **adequate** and suggestions were provided to enhance the draft monograph when applicable
  - **35%** of the NTP authors' responses to reviewer comments were rated as inadequate and recommended revisions were provided





Global Issues

- For both documents, the BSC WG identified among the NTP authors' responses some overarching issues:
  - Issues common to both documents (4)
  - Issues specific to the Draft SoS Monograph (5) or Draft M-A Manuscript (8)
  - These issues might result from an assessment of either "adequate, but" or "inadequate"
- The issues fit broadly into 4 "issue" categories:
  - Scientific issues
  - Sufficiency of information
  - Precision of text
  - Research needs
- Note: Not all BSC WG assessments align to a Global Issue

Presentation of Global Issues

- Demonstrate BSC WG's execution of their charge to assess the NTP authors' responses to the reviewers' comments by
  - Presenting BSC WG assessments that align to Global Issues within each of the four "issue" categories
- BSC WG assessments presented may be for either the SoS Monograph, M-A Manuscript, or both
  - Depends on whether the Global Issue is applicable to the document

Charge:

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*Staff within the Division of Translational Toxicology, National Institute of Environmental Health Sciences developed the Draft SoS Monograph and the Draft M-A Manuscript on behalf of the NTP

Scientific Issues: SoS Monograph

The BSC WG recommends:

clearly summarizing the various studies by identifying inconsistencies as well as consistencies in the Results section.

- **C.28** – The BSC WG notes that the text regarding unexplained inconsistencies in the Results section, page 54, of the draft SoS Monograph is vague. The BSC WG recommends that the authors address their assessment of "unexplained inconsistencies" in the "Unexplained inconsistencies" bullet under "Confidence Assessment of Finding on IQ in Children" instead of discussing "consistency" in the evidence.

- **G.18** – The BSC WG agrees with the reviewer ["For example, on page 36, the statement that 18 of 19 studies provide consistent evidence is a misleading truism, since the 19th study was omitted for being inconsistent. Better to talk about all 19 studies (or 15 study populations) and go from there…."] and recommends that the authors include text in the Results section of the draft SoS Monograph that discusses all 19 studies.

Scientific Issues: SoS Monograph

The BSC WG recommends that:

the Draft State-of-the-Science Monograph contain more discussion about what evidence is and is not available regarding dose/exposure-response between fluoride and adverse neurodevelopmental outcomes, including the importance of both dose/exposure and timing of exposure.

- **G.50** – The BSC WG notes that the Discussion section of the draft SoS Monograph does not address the evidence regarding dose effect or threshold although it concludes that there is an association between higher fluoride and lower IQ in children. The BSC WG does not necessarily agree with the authors that evidence of an association is independent from dose response. Additionally, the BSC WG notes that the authors did not explicitly consider the potential non-linearity of the exposure-outcome association. For example, if there is a non-linear association between exposure and outcome it could be masked in an analysis that does not examine dose response. … At a minimum, the authors should provide a summary of their dose-response analysis from the draft M-A Manuscript in the draft SoS Monograph, with appropriate discussion of uncertainties, especially at 'lower' doses.

- **E.4** – The BSC WG considers the [author's] response a missed opportunity to illustrate an important neurodevelopmental principle and provide greater clarity in the draft SoS Monograph. Any environmental effect on the developing brain is a function of 1) timing and 2) dose/duration (AUC) of the exposure. Inconsistencies in outcome measures often relate to assessing the wrong neurobehavioral domain relative to the timing of the exposure since the outcome is reflective of which brain region and it associated behavioral phenotype is affected.

- **B2.12** – … The BSC WG recommends adding text to the draft SoS Monograph which explains that the strength of the findings is greater at the higher dose range.

Scientific Issues: M-A Manuscript

The BSC WG recommends that:

the Draft Meta-Analysis Manuscript include a statement that acknowledges the lack of a direct measure of dose over time for cumulative exposure and/or critical windows of exposure and that describes the potential effect of this absence on the study conclusions.

- **6a.H** – The BSC WG recommends that the Strengths and Limitations section in the Discussion section of the draft M-A Manuscript include a statement acknowledging the lack of a direct measure of dose and describing its potential impact on the study conclusions. The BSC Working Group recommends text such as: "We acknowledge that the lack of a direct measure of dose limits our ability to determine the shape of the dose-response relationship between fluoride and children's IQ." …

Scientific Issues: M-A Manuscript

The BSC WG recommends that:

the NTP authors closely examine studies that produced a regression slope to determine if they assessed dose response and the shape of the dose-response curve.

- **1.O** – The BSC WG recommends that the authors indicate in the draft M-A Manuscript the shape of the dose-response curve, i.e., how its non-linearity performed (i.e., upward deflection or downward deflection). The BSC WG is concerned that failure to describe any change in the shape of the dose-response curve across the range of fluoride exposure could mask better understanding of the potential inverse association between fluoride and IQ.
- **8.Q** – Because the authors fit a linear term, a threshold was not assessed. Although the authors examined non-linear exposure forms and determined the linear term to be optimal, there are very few data points from studies in the low-dose range, reducing confidence in this range of exposure. The BSC WG recommends that the authors describe any change in the shape of the dose-response curve across the range of fluoride exposures. The BSC WG is concerned that failure to do so could mask better understanding of the potential inverse association between fluoride and IQ.
- **6b.DD** – The BSC WG recommends that the authors provide a potential biological explanation for the shape of the dose-response curves in the low-dose range. If no biologically plausible explanation exists, as the authors have noted elsewhere, then the authors should acknowledge as such in the draft M-A Manuscript.

Scientific Issues: M-A Manuscript

The BSC WG recommends that:

the NTP authors explicitly address the adequacy of evidence [both number and quality of studies] in the low-dose range and provide interpretation of those models.

- The BSC WG notes that there are few high-quality prospective studies, few high-quality studies with low fluoride levels (<2 mg/L or <1.5 mg/L), and few studies outside of Asia.
  - **1.K** – … however, the BSC WG recommends that the authors make clear that their subgroups of studies (0 to < 4mg/L); (0 to <2 mg/L); and (0 to <1.5 mg/L) overlap and thus are not independent. The results that the authors present across the subgroups are correlated, and the BSC WG recommends that should be clearly stated. Without a full understanding of the dose-response mean-effects analysis, it is impossible to understand what these results imply.
  - **3.C** – … In addition, the BSC WG recommends that the proposed revised sentence [from the NTP authors' response]: "There is inconsistency in which model is the best fit at lower exposure levels …" would be strengthened by more precise wording that also notes the attenuation of associations as increasingly restrictive exposure thresholds are applied (< 4 mg/L; 2 mg/L; <1.5 mg/L), along with increases in imprecision resulting from few included studies with those exposure levels.
  - **8.U** – The BSC WG recommends that the authors add more interpretation of the models in the low-dose ranges to the Discussion section of the draft M-A Manuscript. …

Scientific Issues: M-A Manuscript

The BSC WG recommends that:

the NTP authors assess heterogeneity and publication bias separately for each of the three types of meta-analyses (mean-effects, dose-response, and regression-slopes) if these three analyses used different statistics from each study. The BSC WG also recommends that the NTP authors more thoroughly describe the potential impact of both heterogeneity and publication bias on the study conclusions.

- **Heterogeneity**
  - **6b.T** – Given the preponderance of evidence comes from one country/region the BSC WG considers the draft M-A Manuscript limited in its ability to investigate heterogeneity by country. … However, the BSC WG recommends that the authors be more explicit about the issue of heterogeneity. … that the authors address the reviewers' concerns and discuss heterogeneity in the Strengths and Limitations section in the Discussion section of the draft M-A Manuscript and how the lack of reduction of heterogeneity in the subgroup analyses affects the conclusions.
- **Publication Bias**
  - **5.I** – While the BSC WG understands that the authors investigated publication bias, that is not the same as describing the potential impact given that they were unable to rule it out. The BSC WG recommends that the Strength and Limitations section in the Discussion section of the draft M-A Manuscript include a statement acknowledging and describing the potential impact of publication bias on the study conclusions. The BSC WG recommends text such as: "We acknowledge publication bias may exist, and if it does, the impact on our study conclusions would be the following: …, etc." …

Scientific Issues: M-A Manuscript

The BSC WG recommends that:

if the authors did a meta-regression analysis that included regression analyses at the study level, the approach should be more clearly stated in the Draft Meta-Analysis Manuscript.

- The BSC WG notes that the dose-response analysis between total fluoride intake and children's IQ that seemingly underlies the NTP authors' conclusions is not well described in the Draft Meta-Analysis Manuscript.
- The BSC WG is under the impression that the dose-response analysis conducted was on data pooled across different studies, rather than analyses of dose response within specific studies.
  - **6a.L** – The BSC WG recommends that the authors add text to the draft M-A Manuscript Supplemental Materials to fully describe the dose-response mean-effects meta-analysis. It is unclear to the BSC WG if this is a study-level analysis akin to a meta-regression or something else. The authors need to clearly describe whether the units of analysis are at the study level or subgroup within study level. A simple example with a table for the studies showing the actual calculations and numbers that went into the regression would help clarify what analysis was conducted. Without this clarification, it is impossible to assess the results and conclusions.

Sufficiency of Information: Both Documents

The BSC WG recommends that:

the timeframe for the literature search be consistent between the Draft SoS Monograph and the Draft M-A Manuscript.

- The M-A Manuscript and the SoS Monograph do not currently cover the same literature timeframe although the meta-analysis was conducted as part of a larger systematic review reported in the SoS Monograph
- Literature cutoff: May 2020 for the SoS Monograph and November 2021 for the M-A Manuscript
  - **SoS Monograph A2.1** – The BSC WG suggests that the authors include discussion of newly published meta-analyses in the Discussion section of the draft SoS Monograph. … The BSC WG suggests that the timeframe for the literature should be consistent between the draft M-A Manuscript and the draft SoS Monograph.
  - **M-A Manuscript 2.D** – The BSC WG suggests that the authors consider updating the literature searches for the draft M-A Manuscript because with a literature cut-off of November 2021, it is out of date. The BSC WG acknowledges that the authors clearly specify a cutoff date; however, given that the search is out of date, the utility of the draft M-A Manuscript may be considered limited. The BSC WG notes that if the draft M-A Manuscript is submitted to a journal for publication consideration, the journal will likely ask the authors to update the literature search. …

Sufficiency of Information: Both Documents

The BSC WG recommends that:

the SoS Monograph and the M-A Manuscript should be complete, standalone documents and not reference each other for information, unless timing for publication can be coordinated, perhaps by NTP publishing both documents.

- The BSC WG notes that if the two documents are not complete, it could be problematic because (1) the SoS Monograph contains the systematic review on which the meta-analysis relies and (2) since neither document is yet to be published, there is no citation to use.
- Examples of NTP authors' responses where one of the two documents is referenced as the source for information:
  - **SoS Monograph C.11** – "The meta-analysis was removed for separate publication … Indeed, the current draft of the meta-analysis is careful to point out that the collective quantitative assessment of the children's IQ studies is based on a systematic review …
  - **SoS Monograph H.23** – "… The Sup02_2022_Prepublication_NTP_Monograph [Draft NTP Monograph (May 2022 version)] refers the reader to the revised meta-analysis document as it provides a quantitative assessment of dose response to further inform this discussion."
  - **M-A Manuscript 2.A** – "Yes, the NTP Monograph on the systematic review of fluoride exposure and cognitive neurodevelopmental health effects is being published first and is referred to and cited by the *Methods* section as follows: 'The search, selection, extraction, and risk-of-bias evaluation of studies for this meta-analysis were part of a larger systematic review.[8]'"
  - **M-A Manuscript 2.G** – "Yes, this information has been considered and [is] available in Appendix E to the prepublication 2022 NTP Monograph."

Key within a comment: Reviewer comments' text **BLACK** | NTP authors' response **BLUE** | BSC Working Group's assessment **ORANGE**
SoS Monograph comments coded by **Letter.Number** | **M-A Manuscript** comments coded by **Number.Letter**

Sufficiency of Information: SoS Monograph

The BSC WG recommends:

reframing or describing why the benchmark of 1.5 mg/L (World Health Organization standard) was used.

- Specific text in the Draft SoS Monograph: "… higher fluoride exposure [e.g., represented by populations whose total fluoride exposure approximates or exceeds the WHO Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride (WHO 2017)] … ."
  - **G.20** – The BSC WG notes, … this [benchmark] is a bit artificial as there are likely sources of fluoride exposure other than water. There needs to be either an elaboration as to just what this benchmark means and how it is related to the studies that were reviewed or consider an alternative way of framing the data.

Sufficiency of Information: M-A Manuscript

The BSC WG acknowledges that:

the NTP authors have, appropriately, explicitly noted that this meta-analysis was not designed to address the broader public health implications (risks and benefits) of water fluoridation in the United States.

- **7.A** – "We do agree that a federal effort to examine the overall cost-benefit (or risk-benefit) of current fluoride exposure and oral health is an appropriate next step, and there is a precedent for this. … In addition to the prepublication 2022 NTP Monograph, the results of our meta-analysis would be a necessary component of a comprehensive effort to quantify risks in any larger public health risk-benefit evaluation of fluoride… ."
- **3.D** – "… However, given the additional analyses and scope of consideration involved, we consider the implications in the public health setting to be deserving of a more comprehensive risk-benefit analysis that is beyond the scope of this effort."
  - … The BSC WG also recommends that the authors provide relevant context to U.S. populations when discussing the potential implications of their analysis ...
- **8.A** – The BSC WG recommends that the authors include context related to U.S. exposures and comment on the lack of U.S. studies in the draft M-A Manuscript. The BSC WG recommends that the authors add text to the draft M-A Manuscript like that in their response: "Although the clarity of effects at lower fluoride exposures is improving, there are no studies on the potential association between fluoride exposures and IQ in children in the United States, and no publicly available nationally representative urinary fluoride levels, making it difficult to make more specific statements about the relevance of our meta-analysis findings to the U.S. population."…

Sufficiency of Information: M-A Manuscript

The BSC WG recommends that:

the authors update the Discussion section to include new relevant literature, such as (but not necessarily limited to):

- Goodman et al. (2022) Domain-specific effects of prenatal fluoride exposure on child IQ at 4, 5, and 6-12 years in the ELEMENT cohort. *Environmental Research*. 211 (August 2022) 112993.
- Veneri et al. (2023) Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environmental Research*. 221 (March 15, 2023) 115239.

Precision of Text: Both Documents

The BSC WG recommends that:

the authors use more precise language when referring to fluoride exposure, i.e., using "relatively high" or "high" instead of "higher" unless the comparator is stated.

- The BSC WG's recommended revised text:
  - **SoS Monograph I.23** – (new text underlined) "Overall, the cross-sectional studies consistently provide evidence that ~~higher~~ relatively high (or high) fluoride exposure is associated with lower IQ scores in children."
  - **M-A Manuscript 8.M** – (new text underlined) "The meta-analysis of 55 studies (45 high risk-of bias-studies and 10 low-risk-of bias studies) that provided mean IQ scores shows that when compared to children exposed to lower levels of fluoride, children exposed to ~~higher~~ relatively high (or high) fluoride levels had statistically significantly lower IQ scores … ."

Precision of Text: Both Documents

The BSC WG recommends:

replacing "exposure measures" with "exposure assessment measures" or "exposure biomarkers" because exposure can be assessed or evaluated indirectly via biomarkers of exposure (e.g., urinary or blood fluoride) and/or drinking water concentrations, but is seldom, if ever directly measured.

- The BSC WG's recommended revised text:
  - **SoS Monograph C.43** – (new text underlined) "The direction of the association between ~~higher~~ high (or relatively high) fluoride exposure and lower IQ in children was consistent across populations, study designs, exposure assessment measures, and types of exposure data (group-level and individual-level)."
  - **M-A Manuscript 2.H** – (new text underlined) "Predefined subgroup analyses were stratified by risk of bias (high or low), study location (e.g., country), outcome assessment, exposure assessment matrix (e.g., urinary fluoride or water fluoride concentrations), sex, and age group."

Precision of Text: SoS Monograph

The BSC WG recommends:

stressing in the Abstract and other appropriate parts that "exposure" refers to **total exposure** to fluoride and not just exposure to fluoride from drinking water.

- **B2.15** – The BSC WG recommends that the authors add text to the Summary, page 82, (and Abstract, page xiii) of the draft SoS Monograph to provide context to the conclusion statement for readers. The BSC WG notes that the conclusion of *moderate confidence* refers to total fluoride exposure relative to the WHO Drinking-water Quality Guideline of 1.5 mg/L. The text should address that total fluoride exposure includes all sources of fluoride, including drinking water.

- **I.2** – The BSC WG considers the authors' statement provided above in response to the comment (bolded above) is an important statement of background information … The BSC WG recommends that adding this statement to the description of the 'purpose/objectives' of the draft SoS Monograph will help avoid misunderstanding by other readers. "While drinking water provides the majority of fluoride exposure in many studies, total exposure can vary widely even in optimally fluoridated areas based on personal habits in the sure of dental products and consumption of beverages such as black tea that can contain fluoride."

- **C.42** – The BSC WG recommends that the conclusion would be clearer if the sentence were rewritten so that the qualifier refers to exposure. The sentence would be edited to read (new text underlined): "This review finds, with moderate confidence, that higher fluoride exposure (i.e., total fluoride exposure that approximates or exceeds the World Health Organization Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride) is consistently associated with lower IQ in children."…

Precision of Text: SoS Monograph

The BSC WG recommends:

replacing “effects” with “associations” throughout to avoid implying causality, which generally cannot be established from single studies.

- The BSC WG’s recommended revised text:
  - **C.41** – (new text is underlined) “Additional studies on outcomes such as attention-deficit hyperactivity disorder (ADHD) and other attention-related disorders, where there is some evidence of an ~~effect~~ association of fluoride exposure would be necessary to critically assess the data.”
  - **C.60** – (new text is underlined) “There is, however, a large body of evidence on inverse associations between total fluoride exposure and IQ ~~effects~~ in children.”

Research Needs: M-A Manuscript

The BSC WG recommends that:

the "call for additional research," which addresses specific limitations in the current state of knowledge noted in reviewers' comments, is appropriate to include.

- **2.P** – The BSC WG suggests that the authors include in the Discussion section of the draft M-A Manuscript the following sentiment (in the authors' own words): "As potential biological mechanisms that could explain the apparent inverse associations between fluoride exposure and IQ remain uncertain (provide appropriate citations), this is an important area for continuing study and deserves a separate analysis and publication expanding on the potential limitations and promising research on mechanisms."…

- **6b.L** – … The BSC WG also agrees with the caveat provided by the authors in the first sentence [of their response] that "targeted research can certainly add clarity to the existing data—particularly at lower exposure levels." … The BSC WG also notes that there are apparently few high-quality prospective studies, few high-quality studies with low fluoride levels (< 2 mg/L or < 1.5 mg/L), and few studies outside of Asia. Thus, the call for additional research ("[there is a need for] … extensive, rigorous, and reproducible research in both animals and humans") called for in this reviewer's comment is appropriate and should not be dismissed by the authors. The BSC WG recommends that this "call for additional research" is appropriate for including in the draft M-A Manuscript, with specific reference to areas where evidence is limited. …

Summary

- The BSC WG reviewed >400 comments and rated the adequacy of NTP authors' responses to each
- Draft SoS Monograph
  - Overall, the BSC WG agreed with most (87%) of the NTP authors' responses to the reviewers' comments on the Draft SoS Monograph, offering suggested edits for a small number (16%) to improve the quality and clarity of the document
  - The BSC WG found 13% of the NTP authors' responses to the reviewers' comments inadequate and recommended revisions.
- Draft M-A Manuscript
  - The BSC WG agreed with most (60%) of the NTP authors' responses to the reviewers' comments, offering suggested edits for 22% to improve the quality and clarity of the document
  - The BSC WG rated about one-third (35%) of the NTP authors' responses inadequate and recommended revisions.
- The BSC WG identified from among the comments/responses some global issues that were related to the science and the documents' sufficiency of information and terminology, as well as areas for additional research

Questions?