

**National Toxicology Program**

**Board of Scientific Counselors**

**May 4 and 16, 2023**

**National Institute of Environmental Health Sciences  
Research Triangle Park, NC**

***Summary Minutes<sup>1</sup>***

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<sup>1</sup> The summary minutes are prepared by a third-party rapporteur that was present during the meeting and has access to the meeting materials, recording, and transcript.

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## 1. Location of Background Materials and Presentations

Background materials and presentations for the Board of Scientific Counselors (BSC) meetings on May 4 and 16, 2023 are available on the National Toxicology Program (NTP) Past BSC Meetings page

(<https://ntp.niehs.nih.gov/events/past/index.html?type=Board+Of+Scientific+Counselors>).

## 2. Abbreviations and Acronyms

ADA	American Dental Association
BSC	Board of Scientific Counselors
BSC WG	Board of Scientific Counselors Working Group
CDC	Centers for Disease Control and Prevention
DTT	Division of Translational Toxicology
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
HHS	U.S. Department of Health and Human Services
IAOMT	International Academy of Oral Medicine and Toxicology
IQ	intelligence quotient
M-A	Meta-Analysis
NASEM	National Academies of Science, Engineering, and Medicine
NFFE	National Federation of Federal Employees
NHANES	National Health and Nutrition Examination Survey
NIDCR	National Institute of Dental and Craniofacial Research
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
SoS	State of the Science

## 3. Attendees<sup>2</sup>

Attendees were present for both May 4 and May 16, 2023, meetings unless indicated otherwise.

### Board of Scientific Counselors

Chair: Kathleen M. Gray, PhD, University of North Carolina, Chapel Hill (in-person for May 4)

Eric Blomme, DVM, PhD, AbbVie

K. Sean Kimbro, PhD, Morehouse School of Medicine

Matthew T. Martin, PhD, Pfizer

John D. Meeker, ScD, University of Michigan

Devon C. Payne-Sturges, DrPH, University of Maryland, College Park<sup>3</sup>

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<sup>2</sup> The meeting was webcast with the listed individuals attending by Zoom unless otherwise noted as in-person. NIEHS/DTT staff are limited to those with a role in the meeting. Public attendees are limited to those presenting oral comments.

<sup>3</sup> Present only for May 4, 2023.

Mark Russi, MD, Yale University  
Veena I. Singla, PhD, Natural Resources Defense Council  
Janet Z. Yang, PhD, University of Buffalo

### **NTP BSC Working Group**

Chair: David L. Eaton, PhD, University of Washington (emeritus) and University of Arizona (in-person for May 4)  
Antonia M. Calafat, PhD, National Center for Environmental Health, Centers for Disease Control and Prevention<sup>3</sup>  
Pamela Den Besten, DDS, MS, University of California, San Francisco<sup>3</sup>  
Stephanie M. Engel, PhD, University of North Carolina, Chapel Hill<sup>3</sup>  
Michael K. Georgieff, MD, University of Minnesota Medical School<sup>3</sup>  
Sally C. Morton, PhD, MSc, Arizona State University<sup>3</sup>  
Ian J. Saldanha, MBBS, PhD, MPH, Johns Hopkins University and Brown University (adjunct)<sup>3</sup>

### **National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP) Staff**

Rick Woychik, PhD

### **National Institute of Environmental Health Sciences/Division of Translational Toxicology (NIEHS/DTT) Staff**

Trevor Archer, PhD (in-person for May 4)<sup>3</sup>  
Milene Brownlow, PhD (in-person for May 4)  
Kelly Shipkowski, PhD (in-person for May 4)<sup>3</sup>  
Robert Sills, DVM, PhD<sup>4</sup>  
Mary Wolfe, PhD (in-person for May 4)

### **Other Federal Agency Staff**

Gonçalo Gamboa da Costa, PhD, U.S. Food and Drug Administration (BSC liaison)<sup>3</sup>  
Christina Lawson, PhD, National Institute for Occupational Safety and Health (BSC liaison)  
Tucker Patterson, PhD, U.S. Food and Drug Administration (BSC liaison)<sup>4</sup>

### **Contract Support Staff**

Lindsey Green, ICF (in-person for May 4)	Lisa Prince, ICF <sup>3</sup>
Ernie Hood, Bridport Services	Catherine Smith, ICF (in-person for May 4) <sup>3</sup>
Jeanne Luh, ICF (in-person for May 4)	Kit Vinsonhaler, ICF (in-person for May 4)

### **Public Commenters**

Michael Connett, Waters Kraus & Paul  
Paul Connett, on behalf of the Fluoride Action Network  
J. William Hirzy, on behalf of the National Federation of Federal Employees, Local 2050  
Jack Kall, on behalf of the International Academy of Oral Medicine and Toxicology  
David Kennedy, on behalf of the Preventative Dental Health Association

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<sup>4</sup> Present only for May 16, 2023.

Chris Neurath, on behalf of the American Environmental Health Studies Project

Rick North, private citizen

Bill Osmunson, on behalf of Washington Action for Safe Water, King County Citizens Against Fluoridation

Howard Pollick, on behalf of the American Dental Association

## **Day 1: May 4, 2023**

### **4. Introductions and Welcome**

The National Toxicology Program (NTP) convened a meeting of its Board of Scientific Counselors (BSC) on May 4, 2023, via Zoom for identified attendees noted above and by webcast for public attendees. Dr. Kathleen Gray served as chair. Dr. Milene Brownlow served as the Designated Federal Officer.

Dr. Gray called the meeting to order at 12:35 p.m., welcomed everyone to the meeting, and asked BSC members, BSC Working Group (WG) members and chair Dr. David Eaton, Drs. Rick Woychik, Trevor Archer, Mary Wolfe, Milene Brownlow, Gonçalo Gamboa da Costa, Christina Lawson, and staff support in the room to introduce themselves.

### **5. Opening Remarks**

Dr. Rick Woychik, NIEHS and NTP Director, thanked everyone for their participation in the meeting, particularly Dr. David Eaton for all the work he had done over the past year as chair of the NTP BSC WG, Dr. Gray for chairing the current meeting, the BSC members, and the BSC WG members. He reminded everyone that NTP is not a division of NIEHS but is a virtual collaboration between the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA). In his capacity as Director of NTP, he reports directly to Admiral Rachel Levine, MD, who is the Assistant Secretary for Health in the Department of Health and Human Services (HHS).

He provided a brief history of the work conducted by NTP that was under review in the meeting. In 2016, NTP was asked to conduct a systematic review of the literature on the effects of fluoride on children's cognitive development. NTP developed a draft monograph, which was delivered to the National Academies of Science, Engineering, and Medicine (NASEM) for peer review. The peer review committee made several recommendations on how to improve the document and concluded that there was not enough evidence to support its proposed hazard classification for fluoride. NTP revised the monograph to include a meta-analysis, which had been requested by the NASEM committee. The revised draft monograph was subjected to a second round of peer review by the NASEM committee. The committee again concluded that there was not enough evidence to support the hazard classification for fluoride but encouraged NTP to continue to explore the topic. NTP then made the decision to split the document into a State of the Science (SoS) Monograph and a Meta-Analysis (M-A) Manuscript, with the intention of publishing the M-A Manuscript as a peer-reviewed article. Once the draft SoS Monograph was prepared, it was peer reviewed by five external experts as part of the standard NTP peer-review process. Drafts of both documents were reviewed by subject matter experts across HHS.

Numerous comments were received for the two documents and Dr. Woychik decided to delay publication until the comments and concerns could be addressed. He expressed that it was critical to get the science right and with the BSC's role to oversee the quality of the science emerging from NTP, he engaged the NTP BSC to address the comments and concerns from the external peer reviewers and HHS subject matter experts. The BSC did not have the necessary expertise to conduct the review, so in February 2022, the NTP Director and then-chair Dr. Eaton

discussed convening a working group with the requisite expertise to address the comments and concerns. The BSC WG began its work in October 2022 to address the 466 comments and concerns.

Dr. Woychik noted that this meeting was scheduled to review the BSC WG's report and was being held in an open forum in the interest of transparency. Dr. Brownlow then read the conflict-of-interest policy statement and briefed the attendees on meeting logistics.

## **6. Presentation of the NTP BSC Working Group Report**

### **6.1. Summary of Working Group Charge and Process**

BSC WG chair Dr. Eaton provided an in-depth summary of the BSC WG's report to the BSC. He noted that within the federal government there is a process to establish ad hoc working groups to assist standing federal advisory committees such as the BSC to perform fact-finding functions for the committees.

Dr. Eaton reiterated that following the second NASEM peer review, the Revised Draft NTP Monograph was split into the SoS Monograph and M-A Manuscript. The WG had access to:

- Anonymized external peer review and/or federal agency comments on the two documents.
- Draft SoS Monograph (September 2022) and Draft M-A Manuscript (July 2022), which showed track-change edits or referenced (anonymized) specific reviewer comments with NTP authors' responses.
- Revised Draft NTP monograph that went to NASEM (September 2020).
- NTP authors' responses to the NASEM committee's review of the Revised Draft NTP Monograph (September 2020).
- October 2021 and May 2022 versions of the Draft SoS Monograph.

The BSC WG charge was to evaluate the adequacy of NTP authors' responses to external peer review and/or federal agency comments received during development of the Draft SoS Monograph and the Draft M-A Manuscript. It was understood that:

- BSC WG would not provide independent peer review of the two documents.
- BSC WG may offer perspectives and suggest revisions that might improve the quality of either document.

To establish the BSC WG, Dr. Eaton identified the areas of necessary scientific expertise and decided that the WG should consist of no more than 10 members with diverse and appropriate expertise. He solicited suggestions of experts and Dr. Woychik asked for nominations from HHS units. Dr. Eaton considered all the information gathered and identified potential members, who were extensively screened for potential conflicts of interest. Drs. Eaton and Wolfe interviewed each candidate, and then Dr. Eaton made the final selection of individuals to serve on the BSC WG. Dr. Eaton wanted the final selections to reflect overlapping expertise in certain critical areas such as meta-analysis, systematic review, and neurodevelopment/neurotoxicity.

In addition to the BSC WG members in attendance listed above, the WG included:

- Matthew J. Maenner, PhD, National Center on Birth Defects and Developmental Disabilities, Centers for Disease and Prevention.
- David Michaels, PhD, MPH, George Washington University.
- Sharon K. Sagiv, PhD, MPH, University of California, Berkeley.

Review comment sets for both the Draft SoS Monograph and Draft M-A Manuscript were provided to the BSC WG for evaluation. They included:

- 13 sets of reviewer comments (325 comments) with NTP authors' responses on the Draft SoS Monograph.
- Nine sets of reviewer comments (141 comments) with NTP authors' responses on the Draft M-A Manuscript.

All reviewer comments were anonymized regarding the reviewer's identity. The comment sets were coded, and their sources were redacted so that the BSC WG was blinded as to who made the comment, whether an agency or individual reviewer. For the SoS Monograph, each comment was coded by a letter, representing the reviewer, and a number representing that specific comment. The convention was reversed for the M-A Manuscript and each comment was coded by a number representing the reviewer and a letter representing that specific comment.

Dr. Eaton reviewed and assigned each comment to two members of the BSC WG based on the subject matter of the comment and the members' scientific expertise. BSC WG evaluator pairs reviewed each comment and assessed the adequacy of NTP authors' response. If either one of the members of an evaluator pair had concerns, then that comment was discussed by the full BSC WG who then decided together how to respond to that comment.

For each of the 466 comments, the BSC WG rated the NTP authors' response to the reviewer's comment by assigning one of three statements for both documents:

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

If both evaluator pairs deemed the response adequate, it generally was not discussed further unless there were similarities to a previous comment, in which case it was reviewed for consistency.

2. The BSC WG considers the NTP authors' response to the reviewer's comment to be adequate but makes the following suggestion(s) to enhance the "SoS Monograph/M-A Manuscript"<sup>5</sup> document.

- The BSC WG suggests...

In many instances, the suggestions were text from the authors' responses, and the BSC WG suggested that the authors add that information to the document to provide clarity.

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

- The BSC WG recommends...

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<sup>5</sup> The statement would fill-in either SoS Monograph or M-A Manuscript.



Recommendations included revising the text and/or providing additional information to better address reviewers' comments and/or improve the document.

The BSC WG report is organized into three chapters and three appendices. Chapter One is an introduction and summary of the assessment, Chapter Two focuses on the SoS Monograph, Chapter Three focuses on the M-A Manuscript, and the appendices are the SoS Monograph (September 2022), M-A Manuscript (July 2022), and BSC WG members' bibliographies.

The reviewers' comments, NTP authors' responses, and WG's assessments are presented in the report in a standard format, using a color-coding organization system. Black color coding represents the reviewer's comment, blue represents the NTP authors' response, and orange represents the BSC WG's assessment.

Dr. Eaton provided an example of each assessment: adequate, adequate but (with suggestions), and inadequate (with recommendations). Overall, for the SoS Monograph, 87% of NTP author's responses to the 325 reviewer comments were rated adequate, including approximately 16% rated adequate but with suggestions provided to enhance the document when applicable; 13% of the responses were rated inadequate with recommended revisions provided. For the draft M-A Manuscript, 65% of the NTP authors' responses were rated adequate, including 22% rated adequate but with suggestions provided to enhance the document when applicable; 35% of the responses were rated inadequate with recommended revisions provided.

The BSC members had no clarifying questions about the process.

## 6.2. Global Issues

The BSC WG binned some assessments into global issues based on many reviewers having similar comments in various places across the documents. The WG identified issues common to both documents (4) and issues specific to the SoS Monograph (5) or M-A Manuscript (8). These issues might have resulted from an assessment of either adequate but or inadequate.

The issues fit broadly into four "issue" categories:

- Scientific issues.
- Sufficiency of information.
- Precision of the text.
- Research needs.

Dr. Eaton presented the global issues as related to the four "issue" categories. He provided specific examples of BSC WG assessments for each of the global issues as they pertained to both documents and recognized that not all assessments fit, rather these examples highlight the process.

Dr. Eaton reiterated that the charge for the BSC WG was to evaluate the adequacy of the NTP authors' responses to comments, that it was not to do independent peer review, and that the purpose was to ensure that the authors were responding with edits that were scientifically justifiable and appropriate to enhance the scientific veracity and clarity of the two documents.

### **6.2.1. Scientific Issues**

Dr. Eaton presented the global issues that fit in the “Scientific Issues” category along with examples for those issues using the BSC WG’s assessments to specific reviewer comments and corresponding NTP authors’ responses for both the SoS Monograph and M-A Manuscript.

For scientific global issues in the SoS Monograph, the BSC WG recommended the NTP authors:

- Clearly summarize the various studies by identifying inconsistencies in the evidence, not just consistencies, in the Results section.
- Include more discussion about what evidence is and is not available regarding dose, timing, and dose response between fluoride and adverse neurodevelopmental outcomes, including the importance of both dose effect and timing of exposure.

For Scientific Issues in the M-A Manuscript, the BSC WG recommended the NTP authors:

- 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 describes the potential effect of this absence on the study conclusions.
- Closely examine studies that produce a regression slope to determine whether they assessed dose response and the shape of the dose-response curve.
- Explicitly address the adequacy of evidence, both number and quality of studies, in the low-dose range and provide interpretation of those models.
- 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. More thoroughly describe the potential sources and impact of both heterogeneity and publication bias on the study conclusions in the Strengths and Limitations section of the M-A Manuscript.
- More clearly describe the approach if the meta-regression analysis included regression analysis at the study level.

### **6.2.2. Sufficiency of Information**

For Sufficiency of Information in both documents, the BSC WG noted that the documents do not cover the same literature timeframe. The SoS Monograph cutoff was May 2020, whereas the M-A Manuscript cutoff was November 2021. The BSC WG recommended the following:

- The period for the literature search should be consistent between the Draft SoS Monograph and Draft M-A Manuscript.
- The SoS Monograph and the M-A Manuscript should be complete, stand-alone documents and not refer to each other for information unless the timing for publication can be coordinated, which could be accomplished by NTP publishing both documents.

Specifically, for Sufficiency of Information in the SoS Monograph, the BSC WG recommended the following:

- Reframe or describe why the fluoride exposure benchmark of 1.5 mg/L (World Health Organization guideline for drinking water quality) was used, what it means, and how it

relates to the studies reviewed, or consider a different way to frame their data and conclusions around this dose.

Specifically, for Sufficiency of Information in the M-A Manuscript, the BSC WG:

- Acknowledged that the NTP authors 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.
- Recommended that the authors update the Discussion section to include new relevant literature, such as but not limited to Goodman et al. (2022)<sup>6</sup> and Veneri et al. (2023),<sup>7</sup> prior to publication. Dr. Eaton noted that these two papers were identified from a quick search (the BSC WG did not conduct a detailed search of the literature) and the WG members consider them highly relevant.

Dr. Eaton concurred that a federal effort to examine the overall cost-benefit (or risk benefit) of fluoride exposure and oral health is an appropriate next step. He also iterated that suggestions were made by the BSC WG regarding extracted text from the NTP author's responses that they thought should be added to the M-A manuscript.

### **6.2.3. Precision of Text**

For Precision of Text in both documents, the BSC WG recommended the following:

- Use more precise language when referring to fluoride exposure, i.e., use “relatively high” or “high” instead of “higher” unless the comparator is stated.
- Replace “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.

Specifically, for Precision of Text in the SoS Monograph, the BSC WG recommended the following:

- Stress in the Abstract and other appropriate parts of the document that “exposure” refers to “total exposure” to fluoride and not just exposure to fluoride from drinking water.
- Replace “effects” with “associations” throughout when referring to relationships between outcomes and fluoride exposures to avoid implying causality, which generally cannot be established from single studies.

### **6.2.4. Research Needs**

For Research Needs in the M-A Manuscript, the BSC WG recommended that it is appropriate to include the “call for additional research,” which addresses reviewers’ comments on specific limitations in the current state of knowledge.

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<sup>6</sup> 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, 112993. <https://doi.org/10.1016/j.envres.2022.112993>

<sup>7</sup> Veneri et al. (2023) Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environmental Research* 221, 115239. <https://doi.org/10.1016/j.envres.2023.115239>

### 6.3. Concluding Remarks

Dr. Eaton summarized the report and the BSC WG's work. He then thanked the BSC members for their attention, Dr. Wolfe, and her contract staff for their efforts in assembling the presentation, and the committee for its considerable efforts.

#### *Clarifying Question*

BSC member Dr. Gray asked Dr. Eaton to comment on the differences between the two documents, particularly in reference to the percentage of adequate responses to reviewer comments as assessed by the BSC WG (87% for the SoS Monograph and 65% for the M-A Manuscript). Dr. Eaton mentioned that a meta-analysis combines original data from multiple different studies. He noted further that inherent to the meta-analysis process is the generation of uncertainty, which results from comparing and combining studies with varying study designs. In epidemiology studies, there is a great deal of uncertainty in how to assess exposure, as there is with using different statistical approaches to pool the data; meta-analysis is therefore a very scientifically complex area.

## 7. Public Comments

Dr. Gray noted that NTP received 12 written public comments, which are available on the meeting web page. These comments were provided to BSC members prior to the meeting. There were nine requests to present oral public comments. Each commenter was limited to five minutes. Following each comment, the BSC members were asked whether they had clarifying questions. Accompanying meeting materials (i.e., video recording and presentation slides) from oral public commenters are available at

<https://ntp.niehs.nih.gov/events/past/index.html?type=Board+Of+Scientific+Counselors>.<sup>8</sup>

#### *First Oral Public Commenter: Michael Connett, Waters Kraus & Paul*

Mr. Connett, an environmental health attorney, indicated that he represents plaintiffs in a federal court case that is currently exploring whether fluoride added to drinking water poses a neurodevelopmental risk. He asserted that, in a 2020 trial during which expert testimony was provided by several scientists, the judge agreed that current science, especially NIH-funded birth cohort studies conducted in Canada and Mexico, raised “serious questions” about the safety of fluoridation chemicals in water. Before rendering a final conclusion, however, the judge wanted to consider the findings of NTP's review and placed the case on hold to await the monograph's release. After filing Freedom of Information Act (FOIA) requests to understand why the release was taking so long, Mr. Connett's group claimed that NTP was pressured by agencies with very strong partisan interests in fluoride, including the CDC's Division of Oral Health and the National Institute of Dental and Craniofacial Research (NIDCR), which have been working with private lobbyists and public relations professionals to discredit NTP's work. Mr. Connett stated that in May 2022, NTP's monograph successfully cleared external peer review and the FOIA documents showed that NTP's scientists considered the monograph ready for publication. He claimed CDC and NIDCR immediately maneuvered to prevent release of the monograph and succeeded in convincing leadership at HHS to suppress the report. Mr. Connett recounted an

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<sup>8</sup> The summary minutes are prepared by a third-party rapporteur that was present during the meeting and has access to the meeting materials, recording, and transcript.

email from Dr. Brian Berridge, former NTP Scientific Director, and asserted that he expressed misgivings about the political pressure to delay or prevent publication of the report. Mr. Connett asserted that the BSC members were assembled there that day because agencies that aggressively promoted the addition of fluoridation chemicals to drinking water for over 50 years did not like NTP’s science-based conclusions.

### ***Clarifying Question***

BSC member Dr. Veena Singla asked Mr. Connett whether the documents obtained via FOIA would be made available, to which he replied that his group would make them available. Dr. Mary Wolfe later clarified that the documents are posted in the [NIH FOIA library](#)<sup>9</sup> under Electronic Records.

### ***Second Oral Public Commenter: Chris Neurath, on behalf of the American Environmental Health Studies Project***

Mr. Neurath began his presentation by stating he supported the BSC WG’s review and concurred with the majority of the 466 comments. Summarizing the findings of the systematic review, he emphasized, would help explain why there has been so much pushback and why the NTP report has been so long delayed. His summary of the NTP findings included:

- “Moderate confidence” of developmental neurotoxicity.
- Large and very consistent body of evidence supports “presumed hazard” conclusion using NTP’s Office of Health Assessment and Translation (OHAT) methodology.
- No safe threshold observed.
- “Moderate confidence” conclusion applies to water fluoride of 0.7 mg/L.

Mr. Neurath concluded his remarks by asserting that given these findings, it was unsurprising the divisions of HHS that promote fluoridation have tried to alter, delay, and suppress the NTP evaluation and requested of BSC members to uphold the scientific integrity of NTP.

### ***Third Oral Public Commenter: David Kennedy, DDS, on behalf of the Preventative Dental Health Association***

Dr. Kennedy echoed other commenters in expressing appreciation for the integrity of the BSC review and its willingness to “follow the science.” Dr. Kennedy asserted that a risk assessment his organization conducted in 1997 concluded there were increased health risks with increasing fluoride intake, consistent with the NTP findings. He also presented data from a public hearing conducted in 2007 by the Los Angeles Metropolitan Water District, with testimony from Dr. Kathleen M. Thiessen of the Center for Risk Analysis at SENES Oak Ridge, Inc. He referenced her comparison of EPA’s reference dose of 0.06 mg/kg/day with water intake data for infants, children, youths, and adults, including information from the National Research Council review (2006), which showed that the human “no-effect” levels are far exceeded by the EPA reference dose.<sup>10</sup> Dr. Kennedy claimed that most of the “no-effect” levels are exceeded by many members

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<sup>9</sup> <https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/freedom-information-act-office/nih-foia-library>

<sup>10</sup> National Research Council. 2006. Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. Washington, DC: The National Academies Press. doi:10.17226/11571. <https://nap.nationalacademies.org/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards>

of the population, just from fluoride at 0.8 ppm in community drinking water, or in other words, EPA's reference dose is not protective for most of the cited health endpoints, including neurotoxicity. When other fluoride sources are included, even more people are expected to exceed the "no-effect" levels. Dr. Kennedy then claimed a 1956 presentation by the Director of Laboratories of the New York City Department of Water Supply, Gas, and Electric stated: "It is obvious from the knowledge of fluoride toxicity that such factor of safety cannot be established when fluoride is added to the public water supply at the level recommended by the proponents of fluoridation." Dr. Kennedy speculated that fluoridation may be one of the causes of the disruption of our society today, linking it to children with learning disorders and other neurological impairments.

***Fourth Oral Public Commenter: Paul Connett, PhD, on behalf of the Fluoride Action Network***

Dr. Connett introduced himself as a retired professor of chemistry who specializes in environmental chemistry and toxicology and has spent the last 27 years researching fluoride's toxicity and the water fluoridation debate. He presented a chronology of fluoride and neurotoxicity studies beginning in 1996 with publication of a what he characterized as a "groundbreaking" animal neurobehavioral study that found effects that could potentially manifest in children as reduced IQ—the author of which, Dr. Phyllis Mullenix, he claimed, was released from her position at the Forsyth Dental Institute after publication of the study. Since then, Dr. Connett has been documenting the ongoing scientific and political exchange on fluoride's neurotoxicity, the most recent of which he asserted has been the attempt by pro-fluoridation entities within HHS to suppress the NTP review. He noted that NTP is not burdened with making policy, so its researchers can focus on the science underlying toxicological issues. He emphasized that it is imperative that this role be protected from special interests by the BSC. He pointed out what he characterized as "a serious mistake" in the BSC WG's review of the NTP report: The BSC WG incorrectly interpreted  $-0.46$  standardized mean difference in the NTP report as "about a half a point in mean IQ" instead of the correct interpretation of about  $-7$  IQ points, because  $0.46$  multiplied by a standard deviation of  $15$  is equal to seven IQ points.

Dr. Connett quoted from a 2023 statement by Dr. Linda Birnbaum, former Director of NIEHS and NTP, where he claimed that she voiced concern about the decision to dismiss results of an external peer-review process because of "political influence in what should be a strictly scientific endeavor." Dr. Connett asked the BSC to protect NTP and NIEHS from political interference and provide one place where "honest science" can inform public health policy and allow the public to have one entity in which they can trust when it comes to the toxicity of chemicals which impact their daily lives. He discussed several studies funded by NIEHS and other federal agencies, which represented a major advancement in the scientific evidence of fluoride neurotoxicity. He noted that all these high-quality studies have been conducted at  $0.6$  or  $0.7$  parts per million.

***Fifth Oral Public Commenter: Rick North, Private Citizen***

Mr. North spoke to his background in nonprofit health management, including 21 years with the American Cancer Society (the last five as CEO of the Oregon chapter) and 7 years with Physicians for Social Responsibility. He noted he is not a physician, scientist, or dentist and was providing comments through the lens of a lay person. He asserted that any chemical added to public drinking water should first be proven safe and that fluoride at levels found in fluoridated

water has not been proven safe. He asserted that, on the contrary, NTP has found substantial evidence of harm. In 2006, the National Research Council published its landmark review, *Fluoride in Drinking Water*, which found unequivocally that “fluorides have the ability to interfere with the functions of the brain and the body.”<sup>11</sup> A 2012 Harvard meta-analysis found that in 26 of 27 studies, children ingesting higher fluoride levels tested an average of 7 IQ points lower.<sup>12</sup> NTP’s recent meta-analysis linked higher fluoride in 52 of 55 studies to lower IQ. Mr. North observed that the consistency is irrefutable, and that “no one can credibly argue that fluoride has been proven safe.” Mr. North asserted that NTP found the link in 18 of 19 highest-quality studies. The BSC WG commented that “there are few high-quality prospective studies, few high-quality studies with low fluoride levels, and few studies outside of Asia.” NTP determined “several of the highest quality studies showing lower IQs in children were done in optimally fluoridated areas, 0.7.” When looking at all the science and all the comments from outside reviewers, NTP concluded “we have no basis on which to state that our findings are not relevant to some children or pregnant people in the United States.” Mr. North claimed that the epidemiologist hired by the EPA to defend fluoridation in the current lawsuit acknowledged what she considered the four strongest studies ever conducted. He asserted that all were funded by NIH; all showed serious cognitive harm; all were from outside Asia; and all were at levels consistent with U.S. fluoridated water. Mr. North concluded that the very foundation of fluoridation, administering a drug through drinking water, is illogical and asked that the report and M-A Manuscript be released by NTP as soon as possible.

***Sixth Oral Public Commenter: Bill Osmunson, DDS, MPH, on behalf of Washington Action for Safe Water, King County Citizens Against Fluoridation***

Dr. Osmunson began his presentation by stating that in 2015, he nominated fluoride to NTP for developmental neurotoxin, cancer, and thyroid reviews. After noting that fluoride exhibits 20 risks and known harms, he said that this review process has been extremely slow. He and other dentists treat dental fluorosis, a known cosmetic and functional harm that results from children regularly consuming fluoride during the teeth-forming years, the damage from which is far more expensive to repair than the cost of preventative treatment. The National Health and Nutrition Examination Survey (NHANES) reported that two out of three children in the United States have dental fluorosis.<sup>13</sup> Dr. Osmunson read aloud what he considered to be the most simple and accurate statement regarding fluoridation, asserting that it was made by EPA scientists: “In summary, we hold that fluoridation is an unreasonable risk. That is, the toxicity of fluoride is so great, and the purported benefits associated with it are so small – if there are any at all – that requiring every man, woman, and child in America to ingest it borders on criminal behavior on the part of governments.”

Dr. Osmunson claimed the recommendations from the BSC WG were good, and added several other arguments of his own:

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<sup>11</sup> National Research Council. 2006. *Fluoride in Drinking Water: A Scientific Review of EPA’s Standards*. Washington, DC: The National Academies Press. doi:10.17226/11571.

<https://nap.nationalacademies.org/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards>

<sup>12</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3491930/>

<sup>13</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5929463/>

- Fluoride is highly toxic with a probable toxic dose estimated at 5 mg/kg body weight. Fluoride is a known neurotoxin; the question is dosage. What is the “no-effect” dosage? What is the benchmark dose? Fluoride is exempt from toxic and poison laws when regulated as a pesticide or drug. Topical fluoride in toothpaste went through the drug approval regulatory process and the label refers to 0.25 mg, which equals a large glass of water. The drug facts include “keep out of reach of children under 6 years of age. If more toothpaste than is used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away. Directions: adults and children 2 years and older, do not swallow.”
- FDA defines a drug, in part, as a substance “intended for use in the diagnosis, cure, mitigation treatment, or prevention of disease.” Fluoride is well known to the public to prevent dental caries. Topical fluoride has FDA's Center for Drug Evaluation and Research New Drug Application approval with a label “do not swallow” reasonably consistent with the M-A Manuscript and most meta-analyses.
- Mothers who are pregnant or want to become pregnant and children under the age of six should, when possible, avoid drinking water with fluoride concentrations over 0.2 mg/L, not swallow fluoridated toothpaste, and avoid foods and beverages high in fluoride. Caregivers of infants should avoid mixing formulas with water containing more than 0.01 mg/L of fluoride.
- NTP recommends an uncertainty and intraspecific factor of 10. NTP needs to protect more than just the statistical “mean.” Some people are chemically sensitive, some do not excrete fluoride as well, and some drink 10 times as much water as the “mean.” Thus, those persons drinking the most water are not protected under the current guidelines.
- NTP reconcile the disconnect or "disagreement" between the SoS Monograph as "safe" at below 1.5 mg/L and the M-A Manuscript data as "not safe" and the FDA which indicate at 0.25 mg as not safe, do not swallow.

***Seventh Oral Public Commenter: J. William Hirzy, PhD, on behalf of the National Federation of Federal Employees, Local 2050***

Dr. Hirzy introduced himself as a former senior scientist in the EPA Office of Pesticides and Toxic Substances for 27 years and a leader of the National Federation of Federal Employees (NFFE) Union for 24 of those years. He asserted the NFFE Union Local 2050 was the first organization in the federal government to call attention to the public health hazards of fluoride.

Dr. Hirzy described the Union’s experience negotiating with management to challenge the established fluoride drinking water standards on the basis of scientific integrity. NFFE Union Local 2050 became aware in the mid-1980s of fluoride’s hazard through public comments and an employee complaint about EPA’s proposed drinking water regulations. The Union conducted an independent analysis and found the EPA health-based standard of 4 mg/L is wrong. Dr. Hirzy claimed that in 2006, the National Academy of Sciences Blue Ribbon Committee came to the same conclusion. He asserted that the Union tried to address this issue, but the Director of the Office of Drinking Water had already gone through the notice and comment process and said the case was closed. He also asserted the Natural Resources Defense Council (NRDC) contacted the Union to join its lawsuit by filing an amicus brief over the inadequate drinking water standards; the Union bargained with EPA management over scientific integrity until 1998; ten years later,



under the National Partnership Council, the Union was able to get EPA to adopt the principles of scientific integrity. However, Dr. Hirzy claimed EPA seemingly ignores them whenever it is convenient to do so. Dr. Hirzy suggested that NTP's five-round peer review of the fluoride monograph, including interested agencies, is undermining the pursuit of scientific integrity. Dr. Hirzy stated that to continue to promote universal ingestion of fluoride would constitute "public health and economic governmental malfeasance of the first order."

Dr. Singla thanked Dr. Hirzy for his comment and offered a clarification, noting that NRDC is not party to any lawsuits related to fluoride, but had submitted amicus briefs in relation to the litigation Dr. Hirzy mentioned; however, the briefs were in support of neither party and were focused on the requirements under the Toxic Substances Control Act.

***Eighth Oral Public Commenter: Jack Kall, DMD, on behalf of the International Academy of Oral Medicine and Toxicology***

Dr. Jack Kall, a practicing dentist for 46 years, is the executive chair of the Board of Directors of the International Academy of Oral Medicine and Toxicology (IAOMT), a nonprofit group with 1,500 members. Fluoride is one of the academy's foci as it is used in the mouth and ingested via fluoridated water, salt, and fluoride supplements. The IAOMT has been especially concerned about recently published studies regarding the neurotoxicity of fluoride, and therefore supports NTP's systematic review. Dr. Kall expressed the IAOMT's disappointment that fluoride-promoting dental interests, both within and outside the federal government, have been trying to influence NTP's findings to defend their policy of promoting water fluoridation. He summarized what he saw as the key findings of the NTP's report:

- That human epidemiological evidence supports the conclusion of "moderate confidence" that fluoride is a developmental neurotoxin.
- That no safe exposure threshold was found for fluoride's effect on IQ.
- That fluoride exposures experienced by pregnant women and children in the U.S. today are within the range for which human studies have found reduced IQ.

The IAOMT agrees with the report's conclusions, believes that the Monograph should have been published on its intended public release date of May 18, 2022, and agrees with the positive comments from the external peer reviewers regarding the integrity of NTP's work. Dr. Kall shared data from the World Health Organization showing that there has been a dramatic decline in tooth decay over the past several decades in countries with both fluoridated and non-fluoridated water supplies. He interpreted the Precautionary Principle to say, "In the face of uncertain evidence, it is important to act in a manner that protects public health."

Dr. Kall closed with the IAOMT's position on fluoride: "In summary, given the elevated number of fluoride sources and increased rates of fluoride intake in the American population, which have risen substantially since water fluoridation began in the 1940s, it has become a necessity to reduce and work toward eliminating avoidable sources of fluoride exposure, including water fluoridation, fluoride-containing dental materials, and other fluoridated products."

***Ninth Oral Public Commenter: Howard Pollick, MPH, on behalf of the American Dental Association***

Dr. Pollick introduced himself as a clinical professor at the School of Dentistry, University of California San Francisco. He is a dentist, board certified in dental public health, and an advisor to the California Department of Public Health. He spoke on behalf of the American Dental Association (ADA). Dr. Pollick stated that community water fluoridation is the controlled adjustment of the natural fluoride content in water to levels recommended by the U.S. Public Health Service to help prevent tooth decay and that fluoride has been a safe and inexpensive way to reduce tooth decay by at least 25% in children and adults for more than 75 years. He claimed that the CDC hailed it as one of the 10 great public health achievements of the 20th century.

Dr. Pollick said, first, the public deserves to know that its research agencies are not arbitrarily changing peer reviewers when the results are not to their liking. He claimed NTP began the process by asking NASEM to serve as peer reviewer, as the acknowledged gold standard for reviewing complex scientific issues. After the NASEM committee reported that the first two drafts would not survive scientific scrutiny without major revision, Dr. Pollick asserted NTP abandoned that course and instead hand-picked its own panel, which is not consistent with a truly independent peer review. He added that NTP has not resolved what the NASEM committee had identified as worrisome inconsistencies in its risk of bias determinations. Second, he questioned why NTP had been so averse to adding a disclaimer, as the NASEM committee had recommended, clarifying that its literature review did not validate the hypothesis that consistent exposure to low levels of fluoride impacted IQ. The lay reader would have difficulty recognizing that the report's findings are limited to fluoride exposures more than double what the U.S. Public Health Service recommends for community water fluoridation. Finally, he asserted that even if the NTP report was published today, it would already be out of date. Dr. Pollick claimed NTP's finding is based on 19 studies, and at least nine more have been published since the study period ended in 2020 including two meta-analyses; one of the meta-analyses found that "the limitations of most studies raise uncertainties about both the causal nature of such fluoridation and the exact thresholds of exposure involved. Such key issues can only be confirmed by additional high-quality, longitudinal studies."<sup>14</sup> Dr. Pollick said the current state of the science does not validate the hypothesis that fluoride exposure is consistently associated with lower IQ in children and that the ADA generally supports the BSC WG's recommendations regarding the M-A Manuscript. At a time when public trust in federal research is declining, the ADA urges NTP to consider whether this report is consistent with the White House Task Force on Scientific Integrity's recommendations for federal agencies to improve their research processes and adopt better methods of communicating scientific findings to lay audiences. Dr. Pollick said that because there is no compelling scientific or public health reason for rushing the report's publication, NTP is urged not to publish it until ADA's concerns are resolved.

***Clarifying Question***

Dr. Gray asked Dr. Pollick to restate the disclaimer he suggested should be included. Dr. Pollick stated, "The findings do not support consistent evidence of the effects of low fluoride

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<sup>14</sup> Veneri et al. (2023) Fluoride exposure and cognitive neurodevelopment: Systematic review and dose-response meta-analysis. *Environmental Research* 221, 115239. <https://doi.org/10.1016/j.envres.2023.115239>

concentrations in water, below 1.5 mg/L, with IQ.” Dr. Gray thanked the commenters and ended the oral comment period.

## **8. BSC Deliberation on the NTP BSC Working Group Report**

Dr. Gray began the deliberation portion of the meeting by reiterating the charge to the BSC to frame the discussion:

To evaluate the adequacy of NTP responses to external peer review and/or federal agency comments received during the development of both the SoS Monograph and M-A Manuscript.

Dr. Gray asked Dr. Eaton and the BSC WG members to discuss the differences between the SoS Monograph and M-A Manuscript to better support a conversation on the meta-analyses conducted and reviewed as a part of the BSC WG efforts. Dr. Eaton noted that he has limited expertise in meta-analyses, which are complex and statistically challenging. He emphasized that the largest challenge the NTP authors and BSC WG faced was how to construct a meaningful dose-response curve from the data gathered across studies and to infer the shape of that curve. This process assumes a lot of uncertainty. The authors assumed a linear response, and a question was raised as to whether that assumption was justified. Dr. Eaton asked BSC WG members in attendance to weigh in on how the NTP authors might have been able to do a better job of discussing the strengths and limitations of the dose-response analysis from a scientific, statistical perspective.

Dr. Sally Morton, a professor of statistics at Arizona State University with experience and expertise in meta-analysis, said the challenge was one of heterogeneity in the studies, which is always a challenge in meta-analysis. The BSC WG asked for more detail on this point, as well as on publication bias, and suggested that the NTP authors articulate more clearly what the impact of heterogeneity and publication bias might be on the results. Regarding the dose-response model, the BSC WG’s comment was that it is difficult to understand what model was applied, given the information in the manuscript. Dr. Morton herself found it difficult to understand how the model was constructed, whether it was at study level, or how they were conducting the meta-analysis. The challenge that meta-analysts have is that they are limited by the data and by the studies available, which limits testing options such as a quadratic curve or linearity.

Dr. Stephanie Engel, a professor of epidemiology at the University of North Carolina at Chapel Hill, commented on an observation that perhaps the BSC WG had more disagreement with some of the NTP authors’ responses to the meta-analysis versus the SoS Monograph. She cautioned against assuming that these disagreements were because they thought the M-A Manuscript was a substantively worse document. She noted that the BSC WG was only reviewing the reviewers’ comments, so the number of disagreements was due to the nature of the comments for the M-A Manuscript, which were more specific. The BSC WG found that there were more issues for which better clarity could improve understanding. Their charge was to respond to the NTP authors’ response, not to evaluate the manuscript.

Dr. Gray noted that in the cases when the responses were deemed inadequate, it was because of content from the NTP authors that should have been brought into the document. She asked Dr. Eaton to elaborate on this point.

Dr. Eaton reminded everyone that the BSC WG's fundamental task was to try to help the NTP authors make the documents as scientifically strong as possible. He said meta-analyses are an order of magnitude more complex in interpretation, with many more uncertainties relative to the SoS Monograph. Because the SoS Monograph relied on the M-A Manuscript for many of its conclusions, it is quite important to get the M-A Manuscript right. The BSC WG provided guidance and suggestions as to how NTP authors could make the M-A Manuscript stronger and more scientifically defensible.

Dr. Gray reminded the BSC that there would be a motion to decide whether to accept the BSC WG report as written, to accept the report with revisions, to reject the report, or to offer other recommendations.

BSC member Dr. Eric Blomme congratulated the BSC WG on its work. He noted there had been a recommendation during the public comments that the literature should be updated given that in the last two or three years, additional important studies have been published, and asked what the implication would be for the meta-analysis. Dr. Eaton responded that this challenge is difficult to address and that the BSC WG stopped short of saying the authors must redo the meta-analysis but noted the authors should add to the Discussion what they found in the new meta-analyses of the same data. He noted further that the authors should discuss their findings in the context of newer data, even if those data were not included in their initial meta-analysis. He added that the BSC WG had spent considerable time discussing the issue and noted that it was not necessary to re-do the meta-analysis. He emphasized that the BSC WG wanted to guide NTP authors in a course that could be completed in a timely manner and would not entail starting from scratch. Dr. Blomme agreed with Dr. Eaton's comments, noting the need to find balance and the utility of acknowledging the findings in the Discussion. Dr. Eaton added that the NTP authors can discuss, for example, the strengths and weaknesses of their work, new meta-analyses published in the last two or three years, how the results agree or disagree, and openly discuss the challenges of conducting meta-analyses. He reiterated that he and the BSC WG did not think redoing the meta-analysis was the right approach. BSC member Dr. Devon Payne-Sturges concurred and appreciated that the question was discussed. Dr. Gray noted that the BSC seemed to reach agreement that the meta-analysis does not need to be redone.

Dr. Singla asked about the error raised by public commenter Dr. Paul Connett, regarding a possible misinterpretation by the BSC WG of the  $-0.46$  as IQ points instead of standardized mean difference. She suggested investigating whether that IQ number needs to be corrected. Dr. Eaton agreed and said it was already under discussion. Dr. Morton indicated this data check would be conducted to determine whether there was an error in the BSC WG report.

BSC member Dr. John Meeker expressed appreciation of the level of detail provided by the BSC WG members in their comments and agreed the report would need to be acted on as quickly as possible. He said it was clear the BSC WG is narrowing in on getting the language in the documents right.

Dr. Gray circled back to the four key global issues Dr. Eaton had presented for both the SoS Monograph and M-A Manuscript. The first was Scientific Issues with discussion around dose-response relationships, timing, cumulative exposure, dose response curve, and the issue of heterogeneity. Dr. Eaton said that the issues raised were most often identified by more than a single reviewer, and the BSC WG had agreed that they needed to be addressed before the report

is released. He said there is no way to have a perfect document because there will always be uncertainty, debate, and discussion. Dr. Eaton further clarified that rather than pointing out errors, the feedback highlighted uncertainties and areas that needed clarification or that the science behind their conclusions needed more context.

Dr. Gray turned to the second key issue, Sufficiency of Information, particularly the publication of the SoS Monograph and M-A Manuscript as stand-alone documents. Dr. Eaton said it would be problematic to publish them separately, as each document relies on the other, unless the timing was somehow coordinated, with the SoS Monograph published through NTP and the M-A Manuscript published in a peer-reviewed journal. He said the BSC WG noted a potential way around that issue would be for NTP to publish both documents rather than submitting the Manuscript to a journal for additional peer review. They could be published as stand-alone documents, although that approach would require additional modifications to both documents and lead to some redundancy (which might not necessarily be a bad thing).

Precision of Text was the next key issue Dr. Gray mentioned. She appreciated that the BSC WG went to great lengths to make suggestions that resulted in more precise text.

The final issue was Research Needs. Dr. Eaton noted it is always easy to say that we need more research and that he understands that perspective, but that they had also heard from public commenters asserting there is enough research. What the authors need to do, and what these documents can do, is put what is known now in the context of what is important to assessing potential risks. He then reminded everyone that the document was never intended to be a risk-benefit analysis of fluoride in drinking water, but rather an assessment of the scientific evidence for an association between neurodevelopmental effects and fluoride.

BSC member Dr. Matthew Martin addressed the relationship between the M-A Manuscript and the SoS Monograph. He asked for clarification of a passage on page 15 of the July 2022 Draft M-A Manuscript, which stated the Manuscript “extends the findings of our larger systematic review,” and specifically whether the meta-analysis extends the findings of the systematic review versus feeds into the conclusions. Dr. Eaton replied that as he recalled, the authors were noting that their meta-analysis was consistent with previously published meta-analyses by other authors, but since then, additional meta-analyses have been published and NTP authors would need to extend their discussion to include these new studies.

Dr. Gray asked whether members of the BSC WG would be available when NTP authors responded to their recommendations, and if so, what the process would be. Dr. Wolfe replied that NTP authors would work with the chair, who would then reach out to the appropriate BSC WG member. Dr. Woychik commented that it would be enormously beneficial if the BSC WG would be willing to continue working with him and NTP. Dr. Gray clarified that she was not suggesting extended service from BSC WG members but thanked Dr. Eaton for his willingness to be a resource for further clarification. Dr. Eaton said there would undoubtedly be items in the BSC WG report that are unclear, and he would work to clarify or go to the appropriate BSC WG member(s) as needed. Dr. Woychik added that this process is complicated, and he would need the assistance of the advisory groups, both the BSC and the BSC WG, to help with decision-making on complex issues, such as risk of bias. Dr. Eaton said he and the BSC WG members tried to make as clear as possible their noted concerns, though they cannot commit to being peer

reviewers. Dr. Woychik clarified he was mentioning the topic in this public session as he is not allowed to discuss it privately with BSC members.

Dr. Gray closed the discussion by noting the global issues that surfaced arise with many different compounds, contaminants, and chemicals, and there is ongoing dialogue about many of the key issues highlighted in the report. She noted appreciation of the BSC WG's efforts to provide specific recommendations on these complex topics.

### ***BSC Action***

Dr. Gray asked the BSC for a motion regarding the BSC WG report. The options for a motion were to accept the BSC WG report as written, to accept the report with revisions, to reject the report, or to offer other recommendations.

Dr. Singla moved to accept the report with the potential correction to the issue raised by Dr. Connett related to an IQ statistic. Dr. Blomme seconded the motion.

BSC member Dr. Sean Kimbro moved to amend the motion to add discussion of the new meta-analysis findings to the documents. Dr. Blomme seconded the addition to the motion, noting it was already included in the BSC WG report. Dr. Eaton clarified that discussion of new meta-analyses was already included in the BSC WG report and therefore did not need to be part of a motion.

The BSC voted unanimously in favor of the initial motion.

Dr. Gray noted that, as chair, she would formally communicate the recommendations to the NTP Director.

## **9. Closing Remarks**

Dr. Gray asked Dr. Archer to close the meeting by discussing the next steps in the process. Dr. Archer thanked the members of the BSC WG and the BSC members for their efforts and public participants for their comments. He noted that once the chair of the BSC transmits the final report to Dr. Woychik, the recommendations will be carefully considered, and a decision will be made by NTP leadership to address the report as presented. He thanked the BSC WG members and Dr. Eaton for chairing and organizing, recognizing the contributions of Dr. Wolfe and the contract support team for their efforts to organize a comprehensive review in a clear and timely manner.

## **10. Adjournment**

Dr. Woychik thanked Dr. Gray and all members of the BSC and the BSC WG for a job well done. Dr. Gray echoed thanks to Dr. Eaton and the BSC WG. Dr. Brownlow added her thanks to everyone involved in the meeting.

Dr. Gray adjourned the meeting at 3:43 pm, May 4, 2023.

## Day 2: May 16, 2023

### 11. Introductions

NTP convened a follow-up BSC meeting on May 16, 2023, via Zoom for identified attendees noted above and by webcast for public attendees. Dr. Gray served as chair and Dr. Brownlow served as the Designated Federal Officer.

Dr. Gray called the meeting to order at 3:00 p.m. and welcomed everyone to the meeting. She performed a roll call to confirm the presence of BSC members and the BSC WG Chair at the meeting. Dr. Brownlow then asked Drs. Rick Woychik, Robert Sills, Mary Wolfe, Tucker Patterson, and Christina Lawson to confirm their presence.

Dr. Brownlow read the conflict-of-interest policy statement and briefed the attendees on meeting logistics.

### 12. NTP Board of Scientific Counselors Working Group's Review of Text Related to an IQ Statistic

BSC WG chair Dr. Eaton began by noting that this meeting is a continuation of the BSC meeting held on May 4, 2023, when the BSC voted to approve the BSC WG report on the Draft SoS Monograph and the Draft M-A Manuscript on Fluoride in full, with the exception of text related to an IQ statistic (8.P, page 323 of the BSC WG report) that was potentially misinterpreted by the BSC WG. The BSC asked the BSC WG to verify or correct the text.

Dr. Eaton displayed the text in question and noted the comment related to the utility of using a standardized mean difference versus IQ points. The NTP authors responded to the reviewer comment noting that, "...total fluoride exposure among individuals living in optimally fluoridated areas (0.7 mg/L in drinking water) may be higher than 0.7 mg/L, dependent on personal behaviors and habits" and that this type of variation was discussed in the manuscript. The BSC WG agreed that subtle shifts in mean IQ at the population level could have a significant impact and noted that fluoride exposure among individuals in optimally fluoridated areas could be higher or lower than 0.7 mg/L depending on personal behaviors and habits.

Dr. Eaton then highlighted the text under review by the BSC WG, which stated:

"The BSC WG has concern about the next sentence in the Discussion section of the draft M-A Manuscript: 'For example, a 5-point decrease in a population's IQ, would nearly double the number of people classified as intellectually disabled (reference 55).' Table 2 of the M-A Manuscript lists the Overall Mean Effect on IQ in 55 studies as  $-0.46$  ( $-0.55$ ,  $-0.37$ ). Given that the mean effect size is ~ a half a point in mean IQ, that the studies included in the meta-analysis have very indirect measures of exposures (mean effects), and that the heterogeneity in this meta-analysis is very high, the BSC WG recommends that the authors present an example more consistent with their data."

Upon re-review of the data, the BSC WG realized it had misinterpreted the  $-0.46$  as IQ points, when in fact it is the standardized mean difference. One way within an individual study of correlating IQ points with standardized mean difference is to assume the standard deviation for

IQ within a population is 15 points. The standardized mean difference is then multiplied by 15 to give IQ points. In the text under review, a standardized mean difference of  $-0.46$  results in a decrease of approximately 7 IQ points (i.e.,  $-0.46 \times 15 = -6.9$  IQ points). The BSC WG acknowledged the error and proposed deleting the above-referenced section that incorrectly discussed the comparison of the standardized mean difference. Dr. Eaton acknowledged there were many responses provided by the NTP authors, which are not included in this discussion, to comments from peer reviewers about the appropriateness of using this type of calculation when considering many different studies with different designs.

Dr. Eaton called attention to the following text, underlined for the purposes of this presentation: “The BSC WG notes that fluoride exposure among individuals in optimally fluoridated areas could be higher or lower than 0.7 mg/L depending on personal behaviors and habits.” He clarified that underlining lower was not done because lower exposure is more important than higher, but instead to indicate that NTP authors should also note that lower exposure is possible.

Finally, Dr. Eaton noted a clerical error in the BSC WG report in which the word “total” was inadvertently dropped from the text. This correction is important to distinguish total exposure from exposure just through drinking water, which is consistent with other comments the BSC WG has made. The text in question should read: “The BSC WG agrees that subtle shifts in mean IQ at the population level could have a large impact. The BSC WG notes that **total** fluoride exposure...”

### *Clarifying Question*

Dr. Singla asked whether it was correct that the response remained inadequate because it was suggested that the words “or lower” be added. Dr. Eaton confirmed that was correct. He felt that the BSC WG would have no objections if the assessment of the response were changed to “adequate but” with a suggestion to add “or lower,” but that this fell between the lines and the initial recommendation was to maintain the “inadequate” rating. He noted that changing the assessment would require additional changes to the text regarding how many “adequate but” versus “inadequate” responses there were, but this could be updated if needed.

## **13. BSC Deliberation and Action**

Dr. Gray noted that because the current meeting was a continuation of the May 4 meeting, the Federal Register notice did not formally solicit public comment. NTP did receive one written public comment, however, from Chris Neurath on behalf of the American Environmental Health Studies Project. The comment was shared with BSC members in advance and was made available on the meeting web page. BSC members had no comments related to the submission by Mr. Neurath.

### *BSC Action*

Dr. Gray noted there was one item that required a vote, the revised text for Section 8.P. from the BSC WG report. She then reiterated the charge to the BSC:

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



Dr. Gray reminded attendees that the BSC is not providing independent peer review on the SoS Monograph and the M-A Manuscript, and that the BSC may offer perspectives and suggest revisions that could improve the quality of either document. She then asked for a motion from the BSC members present. The options for a motion were to accept the revised text in 8.P as written with the clerical addition of ‘total’ exposure, to accept the revised text in 8.P with revisions, to reject the revised text in 8.P, or to offer other recommendations to 8.P.

Dr. Singla moved to accept the revised text as written with the clerical addition. Dr. Martin seconded the motion. Dr. Gray offered the opportunity for discussion, comments, or questions surrounding the motion. There were none.

The BSC voted unanimously in favor of the motion.

## **14. Closing Remarks**

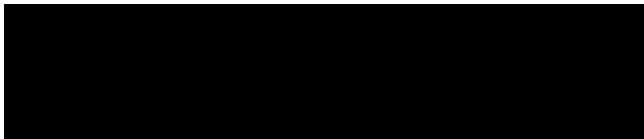
Dr. Woychik thanked Dr. Gray for her leadership and thanked the members of the BSC. Dr. Woychik also thanked Dr. Eaton and the members of the BSC WG in recognition of their efforts and added that the comments raised in the BSC WG report would substantially increase the overall quality of the final manuscripts. He would be working with the NTP authors to make final revisions with the aim of publishing the documents as quickly as possible. Dr. Woychik asked if he could call on the BSC to help resolve any issues that may arise between the authors and the BSC WG’s suggestions. Dr. Gray invited Dr. Woychik to consult with BSC members, who serve as advisors.

## **15. Adjournment**

Dr. Gray thanked Drs. Woychik, Archer, Wolfe, and Brownlow for their efforts, noting her appreciation of the agency’s thoughtful responses to comments. She adjourned the meeting at 3:29 pm, May 16, 2023.

## **16. Approval of the Summary Minutes by the NTP BSC Chair**

These summary minutes have been read and approved by the chair of the May 4 and 16, 2023, NTP Board of Scientific Counselors.



Kathleen M. Gray, PhD, University of North Carolina, Chapel Hill

NTP BSC Chair

Date: