U.S. Environmental Protection Agency Board of Scientific Counselors

Executive Committee

Virtual Meeting Summary

October 26, 2023

Dates and Times: October 26, 2023, 1:00-6:00 p.m. Eastern time

Location: Virtual

Executive Summary

On October 26, 2023, the Environmental Protection Agency's (EPA)'s Board of Scientific Counselors (BOSC) Executive Committee (further referred to as the Committee or EC) convened in virtual meetings. The goals of the meeting were to review and discuss the draft reports on the EPA Transcriptomic Assessment Product (ETAP) and Value of Information (VOI) analysis. The virtual meeting format allowed for presentations, open dialogue, program feedback, Committee deliberations and questions, and EPA responses to questions.

The meeting consisted of two sessions focused on the ETAP and VOI case study and including opening remarks, introductions, overviews of ETAP and VOI analysis, BOSC panel presentations, Q&A sessions, EPA's responses, and panel deliberations.

Mr. Tom Tracy, Designated Federal Officer (DFO), Office of Science, Advisor, Policy, and Engagement (OSAPE) welcomed the EC. He introduced Dr. Maureen Gwinn, Principal Deputy Assistant Administrator and Chief Scientist, Office of Research and Development (ORD). Dr. Gwinn outlined the importance of considering time and resources required to develop EPA product assessment products and suggested the recommendation that VOI analysis be performed on the ETAP product. Dr. Paul Gilman and Dr. Lucinda Johnson, the BOSC EC Co-Chairs, reviewed the meeting agenda and allowed the Committee to further discuss the draft strengths, suggestions and recommendations.

Thursday, October, 26, 2023

Overview of EPA Transcriptomic Assessment Product (ETAP)

Dr. Allison Harrill, Associate Director, Center for Computational Toxicology and Exposure (CCTE) provided an overview of the ETAP draft. Dr. Harrill described that relatively few chemicals have traditional toxicity testing data or human health assessments, and emphasized the time and resources required for a human health assessment using traditional approaches from no toxicity testing data. She introduced ETAP as EPA's new proposal of a human health assessment product based on transcriptomics for data poor chemicals and reviewed the three EPA reports developed for BOSC review. Dr. Harrill summarized the literature review findings of high concordance in point-of-departure (POD) between transcriptomic studies and apical endpoints derived from traditional animal studies. The new ETAP draft human health assessment was developed based on existing NTP reports and datasets. The main components of ETAP development included database and literature surveys, experimental studies and dose response modeling, reference value derivation and reporting. Comparison of transcriptomic reference values with traditional reference doses demonstrated similar levels of protection across a broad

range of chemicals and effects. She explained the streamlined experimental execution, standardized reference value derivation, and defined review process will allow for scalable development and release of human health assessments within nine months of chemical procurement.

BOSC ETAP Panel Presentation and Q&A

Dr. Katherine von Stackelberg and Dr. Craig Rowlands, the BOSC ETAP Panel Co-Chairs, presented the four ETAP Panel charge questions, their findings, suggestions, and recommendations.

Dr. von Stackelberg reviewed the questions the Panel explored to answer Charge Question 1 and discussed the strengths and future considerations. The Panel suggested that EPA periodically evaluate the ETAP methodology and reassess the selected optimal parameters. The six recommendations for Charge Question 1 included clarifications of definitions and consistent uses of specific terminologies, integrating other established methodologies in the selection process of chemicals for the ETAP process, reporting the apical endpoint data on a tissue-specific basis, footnote addition, and specified revisions of the Standard Methods for Development of EPA Transcriptomics Assessment Projects document.

Regarding the proposed uncertainty factors in Charge Question 2, the Panel recommended the method documentation should state that EPA will periodically review the basis for the default uncertainty factors and make the necessary adjustments if justified and revise its statement that default UFs may be decreased when supported by chemical-specific information to say that default UFs may be increased or decreased in such situations.

The Panel supported EPA's proposed approach in Charge Question 3 and recommended the necessity of peer review if EPA decides to depart from the standard approach in exceptional circumstances. The Panel suggested a periodic update and external peer review of the ETAP methodology and reporting.

Pertaining to Charge Question 4, the Panel recommended the addition of some standardized, brief, language to increase clarity and reduce the possibility of misinterpretation of the content and format of the reporting template.

Dr. Tracey Woodruff mentioned that an uncertainty factor greater than 10 may be appropriate to account for susceptible subpopulations and may be applicable in this report. Dr. Richard Becker inquired whether tissues were evaluated for histopathology in the concordance studies. Dr. Craig Rowlands responded that EPA would incorporate this data in the revisions.

EPA Response to ETAP Panel Presentations

Dr. Rusty Thomas, Director, CCTE, thanked the ETAP BOSC for their comprehensive review and comments. He stated that the recommendations will be implemented for these documents.

BOSC EC Deliberation – ETAP

Dr. Paul Gilman and Dr. Lucinda Johnson instructed for the Committee's charge question response to be specific, concise, and actionable in the write ups. Dr. Johnson acknowledged the recommendations and suggested shifting the recommendations for additional tables or

clarification to suggestions. Dr. Justin Teeguarden countered this since the committee members have identified these items as recommendations or suggestions as part of their charge on this BOSC. Dr. von Stackelberg agreed and emphasized the importance for EPA's response because of the impact of ETAP on risk assessment.

Dr. Tracey Woodruff recommended including a reference to the recent National Academy of Sciences (NAS) report titled "Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests." She noted that the findings are relevant to ETAP implementation, though the EPA's ETAP reports were drafted earlier than the NAS report. Dr. Richard Becker suggested maximizing the data gathering when utilizing animal testing and inquired about the justification of the use of animals in this method. The committee discussed whether this was within the scope of the BOSC.

Dr. Gilman instructed the committee to send any editorial suggestions to Tom Tracy.

Value of Information Overview

Mr. Greg Paoli, Principal Risk Scientist, Risk Sciences International, provided an overview of the VOI Case Study. Mr. Paoli introduced the VOI analysis method and explained the application to assess the value of a new assessment paradigm, like ETAP, in relationship to the timeliness of data collection. He described the VOI case study, the flow of the VOI analysis, and the benefits of incorporating both annual risk reduction and timeliness. He described the parameterization of the VOI models for the case study based on empirical data.

Mr. Greg Paoli described the benefit-risk decision-maker (BRDM) and target-risk decision-maker (TRDM) contexts then summarized the case study scenarios. The case study results emphasized the importance of timely decision making, as indicated by the greater public health benefits from the use of ETAP compared to traditional human health assessment (THHA) in different decision-making contexts, for evaluating data-poor chemicals with no existing toxicity or human health data.

Dr. von Stackelberg asked whether 3 or 7 percent discount rates were used in addition to the reported 5 percent. Mr. Paoli explained that the conclusions were not sensitive for 3, 5, or 7 percent. Bart Croes asked whether the incidence of morbidity or mortality was in the millions or billions. Mr. Paoli answered the reduction in risks is in the billions. Dr. Woodruff asked whether if any valuations were missing and Dr. Paoli responded that the analysis was not focused on precise values of specific scenarios but instead on a range from low ($10k/yr) to high ($100k/yr) scenarios.

BOSC VOI Panel Presentation and Q&A

Dr. George Gray and Dr. Julia Rager, BOSC VOI Panel Co-Chairs, presented the four VOI Panel charge questions, their findings, suggestions, and recommendations.

For Charge Question 1, the EC recommended the addition of sufficient method details to enable a knowledgeable reader with access to the data and tools used in the case study to replicate its results such as the BMDExpress input or the dose-response curves for toxicity calculations. The panel recommended a graphical decision tree to clarify the logic of the VOI model and the

incorporating figure 3 in the Hagiwara et al. (2022) paper in the written document of VOI (section 4.2 or 4.3).

Regarding Charge Question 2, the EC recommended the inclusion of a flow chart or diagram to summarize the various sources of information, databases, literature that were used, and which specific variables each data source contributed to in the overall VOI calculations. The Panel recommended clarification on the sources of uncertainty and toxicity distribution information from Chiu et al. (2018) and several sensitivity analyses to explore the influences of time, cost of testing, and control costs. Additional recommendations included clarifications on the benchmark dose (BMD) to benchmark dose lower confidence limit (BMDL) ratios, animal-human toxicokinetic-toxicodynamic, exposure parameterization and partitioning, and the role of each input parameter on the final VOI calculations, and the quantitative characterization of the remaining uncertainty in the ETAP derived toxicity reference value.

Charge Question 3 recommendations included sensitivity analyses on different time durations of the traditional testing/assessment scheme, revisions the text to include more specific information on the steps and timelines associated with each major task within the THHA approach, clarification of whether the sensitivity analyses evaluated effects on the toxicology distributions separately from the effects of varying cost distributions and discussion whether there is a loss of value by not assessing mechanism of action (MOA) or not collecting apical endpoint data in the ETAP study.

Charge Question 4 recommendations included clarification of the steps which chemical categorization or read across data could be integrated in the ETAP approach and using consistent monetary units (millions or billions) in the figures and tables. It is recommended to investigate alternative sources to establish the Annualized Control Cost for the ETAP VOI Case Study.

EPA Response to VOI Panel Presentations

Dr. Rusty Thomas acknowledged this report is technically dense case study/report and expressed appreciation for the VOI Panel's time and effort. He appreciated the feedback to the charge questions for making the report understandable to broader audiences and EPA incorporate the precise wording, clarification, and uncertainty factors in the VOI report.

Dr. Rusty Thomas included that EPA would improve cost control and function and confirmed that were able to interpret the time and cost components for the same. He explained that these were interesting recommendations that would require additional thought.

BOSC EC Deliberations - VOI

Dr. Paul Gilman and Dr. Lucinda Johnson conducted the VOI Executive Committee Deliberation. Dr. Gilman instructed to send the editorial suggestions to Tom Tracy to be reviewed by the Chairs. Dr. Derek Shendell expressed concern about how several recommendations could only be suggestions and wondered if there were too many recommendations. Dr. Julia Rager agreed with his comment and stated they were never given a limit to these recommendations.

Dr. Lucinda Johnson offered to help consolidate recommendations for clarity. Dr. Craig reiterates that EPA needs to include clarification of terms, specific definitions, and maintain consistency through the report.

Closing Remarks and Next Steps

Dr. Paul Gilman, and Dr. Lucinda Johnson, thanked everyone and were pleased with the work of the Agency. Dr. Lucinda thanked the Executive Committee members for their service.

Adjourn Meeting

The meeting adjourned at approximately 4:45 p.m., Eastern Time.

Meeting Agenda and Other Meeting Materials

The agenda[1] and other meeting materials can be accessed at BOSC Executive Committee Meeting: October 2023 | US EPA.

Meeting Participants

BOSC Executive Committee Members:

Paul Gilman, *Chair*

Lucinda Johnson, *Vice Chair*

Richard Becker, PhD, DABT

Bart Croes, PE, MS

Jay Golden, PhD

Daland Juberg, PhD

Rainer Lohmann, PhD

Barrett Ristroph, JD, PhD

Derek Shendell, D.Env, MPH

Justin Teeguarden, PhD

Dana Tulis, MEVE

Stephen Weisberg, PhD

John White, PhD

Laureen Monica Boles, MCP

G. Allen Burton, PhD

Michelle Crimi, PhD

Gilbert Gee, PhD

Jamie Madrigano, ScD, MPH

Ellen Mantus, PhD

Pamela McElwee, PhD

Katharine Jacbos, MLA

Jayne Morrow, PhD

Anjali Mulchandani, PhD

Olga Naidenko, PhD

Mahmoud Saleh, PhD

[1] https://www.epa.gov/system/files/documents/2023-10/bosc-ec-agenda-oct-24-2023-final-draft-v2.pdf

Kevin Teichman, PhD

George Thurston, ScD

Crystal Upperman, PhD, MPA

Tracey Woodruff, PhD, MPH

EPA Designated Federal Officer (DFO): Tom Tracy*, Office of Science Advisor, Policy, and Engagement*

Presenters:

Alison Harrill, *Associate Director, Center for Computational Toxicology and Exposure (CCTE)*

Katherine von Stackelberg, *BOSC ETAP Panel Co-Chair*

Craig Rowlands, *BOSC ETAP Panel Co-Chair*

Rusty Thomas, *Director, Center for Computational Toxicology and Exposure (CCTE)*

Paul Gilman, *BOSC EC Co-Chair*

Lucinda Johnson, *BOSC EC Co-Chair*

Greg Paoli, *RSI, contractor to the U.S. EPA*

George Gray, *BOSC VOI Panel Co-Chair*

Julia Rager, *BOSC VOI Panel Co-Chair*

Other Attendees:

Esra Mutlu	Maureen Gwinn	Michael Miller
Logan Everett	Madison Clark	Elizabeth Sams
Chris G	Annette Guiseppi-Eli	Simone Genna
Linda Wilson	Samantha Jones	Greg Paoli
Maria Hegstad	Candice Lavelle	Mike Devito
Ed Monachino	Chelsea Weitekamp	Christina Baghdikian
Jack Cooper	Mohamed Ghorab	Kelsey Vitense
Andrew Turley	Ruiqin Pan	Leah Wehmans
Jacquelne Heilman	Laura Carlson	Andrew Turley
Matt Klasen	Carinder Malhi	Kris Thayer
Maria Hegstad	Amina Wilkins	Matt Klasen
Pankaj Chawla	Shintaro Hagiwara	Maria Hegstad

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Leah West
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