U.S. Environmental Protection Agency (EPA) Board of Scientific Counselors (BOSC)

Value of Information (VOI) Panel

Virtual Meeting Summary

July 25-26, 2023

Dates and Times: July 25, 2023, 11:00 a.m. to 5:00 p.m.; July 26, 2023, 11:00 a.m. to 5:00 p.m. Eastern Time

Location: Virtual

Executive Summary

On July 25, 2023, the Environmental Protection Agency's (EPA's) Board of Scientific Counselors (BOSC) Value of Information (VOI) Panel convened in virtual meetings. The goal of the 2-day meeting and subsequent teleconferences was to evaluate the VOI framework in a case study by discussing the trade-offs of time, uncertainty, and cost of the EPA Transcriptomic Assessment Product (ETAP). The virtual meeting format allowed for presentations, open dialogue, VOI feedback, panel deliberations and questions, and EPA responses to questions.

Day 1 consisted of opening remarks, introductions, and review of charge questions. Day 1 also included several presentations that provided an overview of VOI analysis and its application to assess the value of a new assessment paradigm, like ETAP, followed by a panel discussion. Day 2 consisted of a panel discussion and included breakout group discussions of the charge questions, followed by a report out from the breakout groups describing their initial responses to EPA's charge questions.

Dr. Maureen Gwinn (Principal Deputy Assistant Administrator and Chief Scientist, Office of Research and Development (ORD)) welcomed the panelists and other meeting attendees. She outlined the ETAP, a new EPA product that uses transcriptomics to assess toxicity for data-poor chemicals in a shorter development time. She underscored the time and resources required to develop EPA assessment products and proposed that the VOI method can be utilized to incorporate the impact of time when performed on the ETAP product.

Dr. Gwinn introduced Mr. Tom Tracy (Designated Federal Officer, Office of Science Advisor, Policy, and Engagement). Mr. Tracy introduced the members of the VOI Panel.

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Dr. Rusty Thomas (Director, Center for Computational Toxicology and Exposure (CCTE)) provided a summary of the application of the VOI framework to evaluate ETAP and the team working on the VOI analysis. He then outlined the agenda and the charge questions for the VOI Panel.

Dr. Alison Harrill (Associate Director, CCTE) summarized the worldwide and domestic chemical and toxicity testing and human health assessment landscape as well as ORD's goal to provide scientific assessments and opportunities for innovation. She then discussed the need for

an additional ORD product for chemicals with limited data that could be applied in a time- and resource-efficient manner and described how ETAP could be a product for this use. She explained the VOI analysis as a method used to provide a more objective decision framework by quantifying the expected gain in economic terms when assessing the trade-offs of time, reducing uncertainty, and cost. She emphasized that the importance of the impact of time in risk assessments and proposed the application of the VOI framework to assess the value of a new approach, ETAP, compared to more traditional approaches.

Mr. Greg Paoli (Principal Risk Scientist, Risk Sciences International) provided an overview of VOI analysis and how it has been used in risk assessment. Mr. Paoli defined VOI analysis as a well-established analytical technique that can be used to determine the "value of information" in systematic terms, and which data generation methodologies are most valuable for risk decision making. He then presented work on a new VOI framework for toxicity testing that took reductions of uncertainty, costs of testing, and delay in obtaining and evaluating data into account. The novel aspect is the inclusion of a time dimension, which permits incorporation of the cost of delays in incorporating additional information. He then outlined how VOI metrics could be calculated, how decisions could be made based on the metrics, and which VOI metrics would be most useful in determining overall utility of the alternative tests being compared.

Dr. Harrill provided an overview of the VOI case study for ETAP. Dr. Harrill stated that the objective was to evaluate the human health and economic trade-offs associated with the timeliness, uncertainty reduction, and costs of different toxicity testing and assessment approaches. The case study focused on two testing methods: (1) a 5-day, repeated dose in vivo transcriptomic study and the ETAP process, and (2) a 2-year rodent chronic toxicity test with traditional human health assessment (THHA) process. Dr. Harrill outlined the uses of features testing process and summarized the proposed ETAP. She then described the study design for VOI analysis, discussing baseline and sensitivity scenarios and VOI metrics assessed.

Mr. Paoli described the parameterization of the VOI models for the case study. The VOI analysis required information on toxicity testing and exposure assessment, economic evaluation, and benefit and costs assessment. Mr. Paoli summarized sources of uncertainty in both ETAP and THHA processes, partitioned exposure assessments, provided an economic evaluation, created a model to minimize the social costs and evaluated a target risk level. Additionally, the analysis required parameters for the baseline and sensitivity analysis. The parameters used in the sensitivity analysis were exposure scenarios, toxicity distribution, economic valuations, target population size, target risk level, and uncertainty associated with ETAP. A total of 306 scenarios were considered in this case study (18 baseline scenarios and 298 sensitivity analysis scenarios). These scenarios provide a range of possible outcomes for results for data-poor chemicals.

Dr. Shintaro Hagiwara (Risk Analyst, Risk Sciences International) provided the results from the case study, describing scenarios from both the baseline and sensitivity analyses. Eight of the nine baseline scenarios produced greater delay-adjusted VOI values than THHA. Changes in the mean exposure level had a greater impact on VOI metrics than variability in the exposure level. In most sensitivity scenarios, ETAP was preferred over THHA, including analysis of parameters for exposure, cost, toxicity, population size, and discordance sensitivities.

Dr. Harrill provided a summary of the VOI case study results. The VOI case study provided an opportunity to evaluate the value of a new human health assessment product and to evaluate the utility of the VOI framework. The case study results demonstrate that, in most scenarios, the ETAP product was the most frequently preferred approach for data-poor chemicals. The results also emphasize the importance of timely decision making. She stated that the VOI framework should be applied in future decision-making contexts.

Dr. Julia Rager (Assistant Professor, Department of Environmental Science and Engineering, University of North Carolina at Chapel Hill), the VOI Panel Co-Chair, facilitated the panel question-and-answer session. There was discussion of how to judge the VOI framework, potential sources of bias in the VOI analysis, and justification of the time costs for each testing scenario. Several panel members described ways to reduce the costs of testing, including evaluating chemical similarity. The panel also discussed the regulatory hurdles that may be faced and how to communicate ETAP as a valuable assessment tool.

Dr. Thomas thanked the panel for their input and closed the session for the day.

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Dr. Annette Guiseppi-Elie (Associate Director of Science, CCTE) welcomed everyone to the second day of the meeting. She described EPA's mission to protect human health and the issue of time and resource management in the assessment of the vast number of chemicals in the environment. She emphasized the capability of ETAP to efficiently assess data-poor chemicals in a timely fashion and VOI analysis as a review of the socioeconomic costs while leveraging the cost of delay in time. She thanked the panel for their time and insights and applauded the work of the VOI analysis team.

Dr. George Gray (Professor of Environmental and Occupational Health, George Washington University Milken Institute School of Public Health), the VOI Panel Co-Chair, led the question-and-answer session. There was discussion of how discordance and adverse events were assessed in the VOI analysis. It was clarified that the total costs did not account for who pays (i.e., government or industry) for the analysis. There was also discussion around guidance on when to choose one testing option over another and the incorporation of mechanism of action into ETAP. Dr. Fred Wright discussed how read-across and quantitative structure activity relationships could be integrated as a tiered approach to assess more chemicals in the VOI analysis.

The panel then entered charge question working groups in a closed-door session. Afterward, Dr. Gray led the report out from the charge question working groups.

For charge question 1, the group concluded that the overall methodology and the results of the VOI analysis provided sufficient evidence to support the assertion that ETAP reduced costs in most scenarios. However, the group suggested improvements, including additional clarity regarding the methodology, graphical representations such as decision trees, deterministic models, and dose-response information.

For charge question 2, the group summarized that evaluation of the input parameters was well informed by global parameters overall, but they felt there should be some consideration of

different classes. Additionally, the group noted that the use of the 20-year time point feels arbitrary.

For charge question 3, the group noted that the scenarios were parameterized with reasonable assumptions and the attempt to evaluate VOI was comprehensive. One point of contention was that the distribution of toxicity may not be normally distributed and that a different distribution may account for outliers. There was also concern for how variability was being used for uncertainties, the binning of exposure into two groups, how the target level is chosen, and how sensitivity may change for different testing durations and schema.

For question 4, the group reported that the VOI framework was well designed and suggested that ETAP was more cost effective in most scenarios. The group felt that there needs to be better explanations of the time needed to complete each test scenario. They assessed that the main drivers of the VOI metrics were time and intra-study variability, and exposure mitigation may not differ between the two approaches. There was also a call for a formal process to explain how VOI analysis will be implemented in assessments more broadly and how stakeholders will be engaged. Finally, the group emphasized that VOI should not be used as a rationale for the replacement of other EPA products, such as THHA.

Dr. Thomas thanked the panel for their input and closed the meeting.

Appendix 1
Meeting Materials & Attendees

Meeting Agenda and Other Meeting Materials

The agenda[1] and other meeting materials can be accessed here.

Meeting Participants

BOSC VOI Panel Members:

George Gray, *Co-Chair*
Julia Rager, *Co-Chair*
Richard Becker
Harvey Clewell
Sean Hayes
Kamin Johnson
Jeffrey Keisler
Dingsheng Li
Igor Linkov
Richard Paules
Leslie Recio
Katherine von Stackelberg
Chadwick Thompson
Timothy Watkins
Fred Wright

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

Presenters:

Chris Frey, *Assistant Administrator for Research and Development, Office of Research and Development*
Maureen Gwinn, *Principal Deputy Assistant Administrator for Research and Development, Office of Research and Development*
Annette Guiseppi-Elie, *Associate Director for Science, Center for Computational Toxicology and Exposure*
Shintaro Hagiwara, *Risk Analyst, Risk Sciences International*
Alison Harrill, *Associate Director of Toxicology, Center for Computational Toxicology and Exposure, Office of Research and Development*
Greg Paoli, *Principal Risk Scientist, Risk Sciences International*
Rusty Thomas, *Director, Center for Computational Toxicology and Exposure, Office of Research and Development*

[1] VOI BOSC Virtual Agenda.pdf (epa.gov)

Other EPA Attendees:

Heidi Bethel
Adam Biales
Tim Buckley
YenWei Chen
Madison Clark
Robert Flick
Sarah Davidson-Fritz
Kathie Dionisio
Peter Egeghy
Beth Ellinport
Logan Everett
Chris Gonzales
Joshua Harrill
Maria Hegstad
Carolyn Holmes
Morgan Hu
Samantha Jones
Hayley Kaplan
Daniel Krewski
David Lattier
Monica Linnenbrink
Esra Mutlu
Jennifer ONeill
Dan Selechnik
Kris Thayer
Scarlett VanDyke
Kelsey Vitense
Sean Watford

Other Attendees:

Rebecca Fry
Xiugong Gao
Gladys Liehr
Gloria Post
Bridget Rogers
Linda Wilson
Carole Yauk

Contractor Support:

Sagi Gillera
Ali Goldstone
Andrew Maresca
Denyse Marquez Sanchez
Sam Snow
Leah West

Appendix 2
VOI Panel Charge Questions

Charge Questions

Q1: The general VOI framework developed by Hagiwara et al. (2022) for comparing human health and economic benefits of toxicity-testing methodologies was adapted for application to this case study. Please comment on the extent to which the VOI framework and decision model are clearly described and the extent to which it provides sufficient representation of chemical risk assessment and decision making that facilitates a reasonable comparison of toxicity testing and human health assessment processes.

Q.2: Most of the inputs to the decision model used in the case study were drawn from published literature sources, experimental measurements, or peer-reviewed computational models. Please comment on the extent to which the input parameters are clearly described and represent the best available sources for use in the case study.

Q.3: The baseline scenarios and sensitivity analyses were intended to represent the range of chemical characteristics and potential uncertainties that could be encountered in applying the toxicity testing and human health assessment approaches to data poor chemicals under EPA regulatory purview. Please comment on the extent to which the baseline scenarios and sensitivity analyses are clearly described and provide reasonable representation of the range of chemical characteristics and potential uncertainties that could be encountered in this context.

Q.4: Please comment on the overall conclusions of the VOI case study that, under the exposure scenarios and assumptions considered, the ETAP is more frequently preferred over the traditional toxicity testing and human health approach for more rapidly and cost effectively evaluating chemicals with no existing toxicity testing or human health data.