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

**Chemical Safety for Sustainability (CSS) and Human Health Risk Assessment (HHRA) Subcommittee**

**Meeting Summary**

**April 10–12, 2019**

**Dates and Times:** April 10, 2019, 8:30 a.m. to 5:30 p.m.; April 11, 2019, 8:30 a.m. to 5:30 p.m.; April 12, 2019, 8:30 a.m. to 2:00 p.m. Eastern Time

**Location:** EPA Research Triangle Park Research Facility, 109 TW Alexander Drive, Durham, North Carolina

## Executive Summary

On April 10–12, 2019, the EPA's BOSC CSS/HHRA subcommittee convened in Research Triangle Park, North Carolina. The goals of the three-day meeting were to review the CSS Research Program's draft Strategic Research Action Plan (StRAP)[1], the HHRA Research Program's presentations and posters, and proposed research strategies therein, and provide advice to the CSS and HHRA programs by responding to several charge questions. CSS and HHRA staff members were available during the meeting to address questions regarding StRAP content and specific areas of input from the BOSC. The meeting format consisted of presentations, open dialogue, EPA program office feedback, subcommittee questions, and EPA responses to their questions.

Days 1 and 2 consisted of presentations and demonstrations showing CSS's eight research areas and HHRA's four research areas, and subcommittee review and discussion of the Agency-provided charge questions, five for CSS and four for HHRA. The subcommittee then formed 3–4 member workgroups to identify strengths, suggestions, and recommendations in response to each charge question. Day 3 consisted of continued discussion between the subcommittee and CSS/HHRA program staff, followed by each workgroup's report-out on draft responses to each charge question.

Dr. Bruce Rodan, Associate Director for Science, Office of Research and Development (ORD), welcomed the CSS/HHRA subcommittee members and noted their role of providing independent peer review of ORD planning and implementation of research. He explained that EPA will make every effort to implement the BOSC's recommendations. Dr. Rodan emphasized that the difference between the CSS and HHRA Research Programs is that the CSS program focuses on research, and the HHRA program examines potential research aspects. Mr. David Dunlap, Deputy Assistant Administrator, ORD, was in attendance. Mr. Tom Tracy served as the Designated Federal Official from ORD.

## CSS Research Topic Overviews, Demonstrations, and Group Discussion

Dr. Jeffrey Frithsen, National Program Director, CSS Research Program, outlined the program's integration of three organizing topic areas, eight research areas, and 48 strategic outputs. He described the CSS program's long-term visions, including providing information needed to

[1] https://www.epa.gov/sites/production/files/2019-02/documents/css_draft_strap_bosc_review_20181221.pdf

inform Agency decisions about chemicals; accelerating the pace of chemical assessment and decision-making; replacing, reducing, and refining vertebrate animal testing; and providing scientific innovation and leadership to transform chemical screening and assessment. He emphasized how the CSS program focuses on partner needs and solutions, specifically surrounding partner-driven research, engagement, and outreach. He concluded by summarizing the CSS program's effort to prioritize needs and resources.

Dr. John Kenneke, National Exposure Research Laboratory (NERL), presented the first research topic overview on chemical evaluation. He explained how there are three research areas within the topic, including high-throughput toxicology (HTT), rapid exposure modeling and dosimetry, and emerging materials and technologies. He noted that the CSS program works to integrate products from the three research areas to provide toxicological and exposure information on thousands of chemicals. Dr. Kenneke also described examples of partner needs for the research topic, which include developmental neurotoxicity research, curation of chemical exposure data from consumer products, and engineered nanomaterials research.

Dr. Joe Tietge, CSS Research Program, described the research topic overview on complex systems science. He noted that the topic encompasses three research areas, including adverse outcome pathways (AOPs), virtual tissue modeling, and ecotoxicological assessment and modeling. He outlined the objectives of the research topic, which are predicting apical outcomes from mechanistic data, new approach methodologies (NAMs) at complex biological scales, and integrative modeling of complex systems and pathways. Dr. Tietge also emphasized how the CSS program utilizes partner-driven cases studies to inform its research. He provided examples of relevant partner needs, including data on emerging contaminants and mixtures, tiered testing strategies, and data on the safety of pesticides for pollinators.

Dr. John Cowden, National Center for Computational Toxicology (NCCT), presented on the solutions-based translation and knowledge delivery research topic. He discussed how the topic's purpose is to aid the translation of CSS program research through partnerships and increase confidence in CSS program approaches, data, and tools for environmental decision-making. The research topic focuses on data delivery, cheminformatics, and predictive models to provide tools, infrastructure, and knowledge, for ORD's partners to use when making risk decisions. The topic has two research areas including chemical safety analytics and chemical informatics, synthesis, and integration (ISI). Dr. Cowden also discussed examples of partner needs for the research topic, one being to help the Office of Pollution Prevention and Toxics (OPPT) establish prioritization approaches that take advantage of new predictive tools and models.

CSS program office partners presented on their collaborations with CSS. Presenters included representatives from OPPT, the Office of Pesticide Programs, the Office of Science Coordination and Policy, the Office of Land and Emergency Management, and the Office of Water. Each speaker gave an overview of their office's research and areas of collaboration with the CSS program.

Dr. Antony Williams, NCCT, presented a demonstration of EPA's CompTox Chemistry Dashboard, which is available at https://comptox.epa.gov/.

CSS/HHRA subcommittee members and EPA staff members engaged in discussion on various subjects surrounding each research topic, including providing data to stakeholders, communicating model and data uncertainties, the use of case studies, and collaboration between CSS and HHRA. Other topics of discussion included chemical mixtures and data/model transparency.

**HHRA Research Area Overviews, Demonstrations, and Group Discussion**

Dr. Tina Bahadori, National Program Director, HHRA Research Program, outlined the program's focus on the practice and conduct of risk assessments. Compared to the CSS program, she explained that the HHRA program emphasizes translational science and improved integration of human and ecological assessment science, both grounded in risk assessment methodologies and systematic review. Dr. Bahadori described HHRA's four research areas, including science assessment development; science assessment translation; emerging and innovative assessment methodologies; and essential assessment infrastructure and support tools. She also discussed the HHRA program's cross-coordination with other research programs within the Agency. HHRA works with the Safe and Sustainable Water Resources and Air and Energy Research Programs regarding wildfires and emerging materials, and closely collaborates with the CSS program on certain tools to gain acceptance in the broader public health community. Some examples of CSS-HHRA collaboration include the RapidTox dashboard and the use of alternatives to animal testing in risk assessment.

CSS/HHRA subcommittee members and EPA staff members engaged in discussion on various subjects surrounding each research topic, including machine learning, the Integrated Risk Information System program, the Superfund Health Risk Technical Support Center, and systematic review tools. Subcommittee members and EPA staff also discussed further collaboration between the CSS and HHRA programs.

Dr. Katrina Waters, BOSC CSS/HHRA subcommittee chair, requested that the subcommittee focus only on feedback alone for the HHRA program, since the subcommittee will not develop a formal report until late summer 2019.

**Subcommittee Discussion of Charge Questions and EPA Response to Questions**

The CSS/HHRA subcommittee discussed each of the five charge questions for the CSS program and the four program-specific charge questions for the HHRA program.

Dr. Waters suggested that the CSS/HHRA subcommittee provide several recommendations. The subcommittee formed 3–4 member workgroups to address each charge question, with the goal to produce draft responses on day 3 of the meeting.

**CSS: Subcommittee Report-Out and Summary of Preliminary Recommendations**

Each workgroup identified strengths, suggestions, and preliminary recommendations pertaining to the draft CSS StRAP and their specific charge questions. The CSS/HHRA subcommittee discussed the recommendations of each workgroup and presented an initial summary for CSS program staff on day 3. These recommendations and supporting suggestions will be reviewed and refined by the subcommittee over the next few months and finalized in a draft report to be reviewed at the BOSC Executive Committee (EC) meeting.

***Charge Question 1a - Does the research outlined for the 2019–2022 timeframe support the relevant Agency priorities as described in the EPA and ORD strategic plans?***

- Look at the workflow to identify key people in partner program and regional offices.
- Do not include synthetic biology as a high priority.
- Interact with states, tribes, and other stakeholders to prioritize research needs.
- Explicitly tie research activities to specific problem formulation/decision contexts of the program offices.
- Consider more explicit integration of integrated approaches to testing and assessment that use biological activity exposure ratio at each decision node.
- Do not de-emphasize early stage life-cycle assessments (LCA) as a decision-making tool along with on-going work.
- Give toxicological evaluation of chemical mixtures, based on common chemical co-exposure, a higher priority.

***Charge Question 1b - Each ORD research program undertook a rigorous engagement process to provide additional detail on specific EPA program and region, state, and tribal needs, the results of which are summarized in the StRAP objectives and explanations of research topics and areas. How well does the proposed research program respond to these partner-identified needs? Going forward CSS should develop a more deliberate/explicit and transparent process to solicit information from partners regarding their needs and priorities as well as to afford opportunities for CSS partners to provide feedback on the StRAPs as they are developed.***

- Develop a more deliberate/explicit and transparent process to solicit information from partners regarding their needs and priorities as well as to afford opportunities for CSS partners to provide feedback on the StRAPs as they are developed.
- Frame and pursue CSS program research as serving the needs of all its partners.
- Define stakeholders and provide more discussion of how their needs were identified and used to inform the StRAP, to the extent the StRAP was designed to be responsive to stakeholder needs in addition to partner needs.
- Ensure research efforts include a focus on methods for HTT for hard-to-test substances.
- Engage more with the HHRA program to identify approaches to validate the correctness of the outcomes of NAMs to build confidence in utilizing those outcomes in place of animal data for risk assessment in the regulatory setting, because a potential major use of the NAM is replacing animal studies for use in risk assessment.
- Implement more formal approaches to engage other stakeholders (e.g., non-governmental organizations, or NGOs) in seeking feedback on the current and expected major environmental health and ecological concerns as well as in disseminating results and capabilities.
- Develop for future StRAPs a deliberate partner engagement plan that details the process that will be undertaken to identify partner needs, recognizing that priorities and needs may shift over time.
- Develop for the current StRAP a partner engagement plan or process to solicit feedback from partners regarding implementation.
- Identify a set of activities that the CSS program will pursue regarding partner or stakeholder education, training, and pilots.

    - Coordinate with the HHRA program to support this effort; they have long-standing touch points with regions and states via Superfund technical supports and could assist with training and educating practitioners on CSS products.
    - Continue Regional Applied Research Effort (RARE); only one RARE project with Region 8 mentioned.
    - Use perfluoroalkyl subsances (PFAS) as an opportunity for education, training, and piloting with partners.
- Develop a set of activities to pursue for broader stakeholder outreach and engagement around CSS program research and products, with the aim of building greater confidence and acceptance of the use of CSS products in risk assessment and regulatory decision-making for the protection of human health and the environment.

***Charge Question 1c - Does the StRAP, including the topics, research areas, and proposed outputs, clearly describe the strategic vision of the program? Given the environmental problems and research objectives articulated, please comment on the extent to which the StRAP provides a coherent structure toward making progress on these objectives in the 2019–2022 time frame.***

- Create a definitive goal or program that is charged with developing and instituting a clear "uncertainty informatics" toolbox that will provide wide acceptance of "new" data and its use in risk assessment.
- Increase as resources become available Science to Achieve Results grants, contracts, and partnerships with other entities inside and outside the government to jointly develop and validate NAMs.
- Work with the program offices to develop a uniform set of scientifically robust yet flexible principles and approaches for establishing scientific confidence for the methods and new data streams to meet the different program office decision contexts. As the models are developed, there should be a joint model performance verification and implementation effort with the program offices designed to develop confidence and encourage use of the tools.
- Partner in the National Toxicology Program Strategic Realignment to develop alternative strategies for carcinogenicity, reproductive, and developmental toxicity testing.
- Discuss ongoing work to address sensitive or highly exposed subpopulations, such as children, workers, affected communities, and others in the StRAP.
- Include early stage lifecycle analysis (LCA) of emerging chemicals, that include not just those then enter the consumer stream but are intermediate agents in manufacturing, is important to forestall potential problems from inadvertent release.
- Describe clearly biological activity profiling.

***Charge Question 1d - Recognizing ORD's focus on addressing identified partner research needs, in the presence of reduced scientific staff and resources, are there any other critical emerging environmental needs or fields of expertise and/or new research methods where this program should consider investing resources?***

- Increase ISI staff to accommodate the need for computational tools that need to be consistently updated and reviewed as new data become available. The efficiency of the process would be improved with machine learning and artificial intelligence.
- Include a focus on health effects in addition to exposure assessments.
- Define the limitations for AOPs for complex and human relevant mixtures.
- Include for the CompTox dashboard approaches to use high-throughput toxicokinetics and in vitro to in vivo extrapolation (IVIVE) to develop biomonitoring equivalents: the concentration in human blood or urine that correspond to the points of departure, provisional peer-reviewed toxicity values (PPRTVs), and reference doses (RfDs).
- Expand ORD CSS program work with the Office of Chemical Safety and Pollution Prevention to evaluate ways to improve methods, models, and scientific approaches in EPA's new chemicals program. EpiSuite was noted as having many issues.
- Explore opportunities to work with relevant program offices to use the high-throughput, new exposure modeling tools to identify potential emerging contaminants. HTT should also include relevant mixtures identified from biomonitoring studies.
- Discuss research needs assessments with relevant program offices.
- Clarify for non-targeted exposure research activities if there is a strategy or rationale for determining what media to focus on. Further, if the overall goal is to interpret the presence of a chemical in a non-targeted sample mean in terms of potential effects on health, define the strategies to go from detection to quantitation to exposure and to risk.
- Explore the integration of AOPs with computer models of biological systems, with the goal of developing quantitative models that include toxicokinetics and a dynamic range of responses, dose-dependent transitions (e.g., tipping points from one key event to the next).
- Communicate complex science to clients, including the public.

***Charge Question 1e - What are some specific ideas for innovation (including prizes/challenges) and market-based approaches that the program could use to advance solutions to existing and emerging environmental problems?***

- Consider developing a challenge or prize program for stakeholders (e.g., NGOs and invested parties) who invest in or use these kinds of tools or outputs.
- Award recognition of programs (similar to Green Chemistry Awards) for parties who use or develop novel tools.
- Incentivize the posting of AOPs through a simplified formatting requirement. It is critical that user interfaces are easy to use and require minimal time and effort to encourage more researchers to contribute.

- Use grant programs to fund development of methods and tools such as the Small Business Innovation Research Program, and collaborate with other funders such as private foundations or other agencies.
- Consider adding training for a subset of members in science communication to the public for preparation of written, web-based, and verbal materials to inform the public of what its outputs are and how it is working to protect environmental health and ecology.

**HHRA: Subcommittee Report-Out and Summary of Preliminary Recommendations**

Each workgroup provided feedback based on HHRA presentations, posters, and their program-specific charge questions. The CSS/HHRA subcommittee discussed the feedback from each workgroup and presented an initial summary for HHRA program staff on Day 3. The HHRA draft StRAP and the subcommittee's feedback will be evaluated in late summer 2019, and finalized in a draft report to be reviewed by the BOSC EC.

***Charge Question 1 - Does the research outlined for the 2019–2022 timeframe support HHRA's ability to deliver the range of assessments the Agency is requiring?***

- HHRA's portfolio approach of tailoring product to question rather that one-size-fits-all assessments is a step forward.
- HHRA's vision for coordinated developments of products with the CSS program (e.g., RapidTox) is excellent.
- Investments in Emerging and Innovative Assessment Methodologies will likely show good returns.
- The use of uncertainty methods is an important advance that will contribute to analysis of future issues dealing with multiple exposure and sensitive populations.
- HHRA program staff need to consider mixtures, particularly in tool development.
- There has been good work towards increasing the efficiency of the systematic review process (e.g., machine learning).
- The HHRA program needs to develop decision making tools that underscore transparency.

***Charge Question 2 - Does the StRAP overview as presented, including the topics, research areas, and proposed outputs, clearly describe the strategic vision of the program? Given the environmental problems and research objectives articulated, please comment on the extent to which the StRAP provides a coherent structure toward making progress on these objectives in the 2019–2022 timeframe.***

- The HHRA program's research areas and proposed outputs align well with the program vision.
- Focus on advancing the research areas of mixtures as well as development applications of CSS program tools.
- Increase case studies for CSS and HHRA program staff to demonstrate the application of products, and develop case studies that may be good demonstrations of future needs of how to incorporate results from the advancement of NAMs.

- The illustration of developing assessments and providing technical support through the two centers—Superfund Health Risk Technical Support Center and Ecological Risk Assessment Support Center—provides tangible evidence of how products are being applied to serve the needs and priorities of their partners, stakeholders, and customers.
- The HHRA program dedicates time to training and interacting with partners (e.g., the Communities of Practice). The workgroup would like to see this further developed in a way that clearly builds up the HHRA program vision. They recommended that the StRAP include concrete examples of how training will be developed and built up in the future.
- There are clear efforts to integrate CSS program products in the practice of chemical risk assessment, and this is a strength (i.e., the posters on NAMS, RapidTox, and Benchmark Dose software). The integration of external tools was also impressive, such as the World Health Organization's Approximate Probability Analysis methodology for calculating probabilistic RfD estimates.
- The outputs seem relevant, but the research activities are not clearly articulated. Research activities should focus around NAMS and consideration of chemical mixtures.
- For the PPRTV poster, the workgroup recommended a research exercise of developing PPRTV using solely CSS program products, potentially through a case study.
- Recognize the strength of existing communication between the CSS and HHRA programs (e.g., the incorporation of NAMS as an integration or stand-alone).
- The use of open-source and shared data software programs such as the Health Assessment Workspace Collaborative important. This will have clear benefits to partners and stakeholders, who will be able to access the data and models and potentially use them for their own purposes.
- There has been an impressive demonstration of increased output and decreased amount of time (e.g., building up literature search capabilities using machine learning). The workgroup encouraged the use of machine learning to streamline approaches as much as possible.
- Continue to integrate environmental human risk assessment with ecological assessment and define how such an integration would be conducted.

***Charge Question 3 - HHRA has been collaborating with CSS on laying the foundation for future risk assessments. Please comment on the extent to which HHRA research is prepared to use novel data streams and tools, such as those from CSS, to advance the future of assessment science.***

- The HHRA program has made good progress in developing risk assessment frameworks and tools that can make use of the CSS program's novel data streams and tools.
- To enhance the utility and efficiency of HHRA work products, the program should develop and institutionalize workflows that are problem formulation driven and fit for purpose so that there is full alignment of HHRA applied research projects with the specific decision contexts of the programs they serve.
- The decision context will inform the complexity of the analyses and the degree to which the HHRA program needs to depend on or utilize the variety of tools and approaches offered by CSS program research.

- Different tools and methods can be selected to achieve the degree of scientific confidence needed for different decision contexts (e.g., priority setting versus screening or in depth).
- Use computational tools and approaches, such as those in Patlewicz et al., 2018, high throughput exposure modeling (ExpoCast/Systematic Empirical Evaluation of Models), and the Threshold of Toxicological Concern to determine margins of safety may provide sufficient scientific confidence for risk-based prioritization.
- For complex, comprehensive assessments, the HHRA program should base the design of such assessments on a systems biology model (or models), such as AOPs or modes of action (MOAs). The new data streams from the CSS program will largely provide biological activity profiling information, including quantitative predictions of bioactivity. Thus, information from such CSS program data streams (e.g., high throughput, high content, biological activity profiling transcriptomics, and high content phenotypic profiling) are anticipated to be most useful in understanding potential bioactivity associated with early or intermediate key events in such systems biology models.
- Look beyond the CSS program and be prepared to evaluate the scientific confidence of other novel data streams and tools and, as appropriate, use these to meet the specific design needs of HHRA program assessments.

***Charge Question 4 - Recognizing ORD's focus on addressing identified partner research needs, are there any other critical emerging assessment-related needs or fields of expertise and/or new research methods where this program should consider investing resources?***

- The presentations at the April 2019 meeting did not clearly reflect that HHRA is prioritizing research on methods that could apply to mixtures or cumulative exposures.
- The BOSC previously commended the HHRA program's research focus on epigenetic and other susceptibility factors in risk assessment this area of research. This issue remains important for improving risk assessments that evaluate children and other vulnerable subpopulations. An epigenomic risk assessment approach should be addressed in the new HHRA StRAP.
- HHRA is making appropriate use of CSS program tools; these efforts should be continued and expanded, with greater interactions among staff in the two programs.
- Systematic review methods development is an important focus of work, and the progress to date is impressive. The HHRA program should focus some effort on the development of methods to better incorporate mechanistic studies into systematic reviews (including grading such studies during the evidence integration phase).
- Consider analyzing the requests that come in from the regional offices and other partners and stakeholders to identify areas of need.

**Conclusion**

The combined responses from each workgroup's recommendations will be compiled into the draft BOSC CSS and HHRA StRAP review reports. The subcommittee will convene via teleconference to discuss the final revisions as a group before the BOSC EC meeting, which will convene in June 2019. The EC will consider the subcommittees' recommendations and finalize the overall BOSC report, which will include reviews of each of ORD's research programs.

**Meeting Agenda and Charge Questions**

The agenda[2] and the draft charge[3] can be accessed at https://www.epa.gov/bosc/chemical-safety-sustainability-subcommittee-meeting-documents-april-10-12-2019.

**Meeting Participants**

**BOSC Chemical Safety for Sustainability/Human Health Risk Assessment Subcommittee Members:**

Katrina Waters, *Chair*
James Stevens, *Vice Chair**
Gina Solomon, *Temporary Vice Chair*
Anthony Bahinski
Richard Becker
Juan Colberg
Richard Di Giulio
Chris Gennings
Dale Johnson
Daland Juberg
Juleen Lam
Timothy Malloy
Jennifer McPartland
Jane Rose
Ponisseril Somasundaran
Donna Vorhees
Clifford Weisel
Mark Wiesner

**did not attend*

**EPA Designated Federal Official (DFO):** Tom Tracy, *Office of Research and Development*

**EPA Presenters:**

Tina Bahadori, *National Program Director, Human Health Risk Assessment Research Program*
Betsy Behl, *Director, Health and Ecological Criteria Division, Office of Water*
John Cowden, *Biologist, National Center for Computational Toxicology*
Alexandra Dapolito Dunn, *Assistant Administrator, Office of Chemical Safety and Pollution Prevention*
David Dunlap, *Deputy Assistant Administrator for Research and Development, Office of Research and Development*
Jeff Frithsen, *National Program Director, Chemical Safety for Sustainability Research Program*
Hayley Hughes, *Director, Office of Science Coordination and Policy*

[2] https://www.epa.gov/sites/production/files/2019-04/documents/bosc_css-hhra_agenda_20190408v3.pdf
[3] https://www.epa.gov/sites/production/files/2018-12/documents/strap_charge_to_bosc.pdf

John Kenneke, *Assistant Laboratory Director, Chemical Safety for Sustainability Research Program*
Anna Lowit, *Senior Science Advisor, Office of Pesticide Programs*
Jeffery Morris, *Director, Office of Chemical Safety and Pollution Prevention*
Kathleen Raffaele, *Senior Science Advisor, Office of Land and Emergency Management*
Bruce Rodan, *Associate Director for Science, Office of Research and Development*
Joe Tietge, *Deputy National Program Director, Chemical Safety for Sustainability Research Program*
Antony Williams, *Chemist, National Center for Computational Toxicology*

**Other EPA Attendees:**

Xabier Arzuaga
David Bussard
Anna Champlin
Brian Chorley
Allen Davis
Ingrid Druwe
David Dunlap
Steven Dutton
Amanda Fitzmorris
Megan Fleming
Jill Franzosa
Lauren Gessner
Jeff Gift
Andy Gillespie
Annette Guiseppi-Elie
Maureen Gwinn
Belinda Hawkins
Dale Hoff
Keith Houck
Samantha Jones
Richard Judson
Barbara Klieforth
Tom Knudsen
Andrew Kraft
Carlie LaLone
Jason Lambert
Meredith Lassiter
Emma Lavoie
Lucina Lizarraga
Mike Loughran
Madison McGovern
Alexa Moore
Jennifer Nichols
Beth Owens
Tom Puruker
Elizabeth Radke-Farabaugh
Sandy Raimondo
Bruce Rodan
Kim Rogers
Paul Schlosser
Anita Simha
Todd Stedeford
Michele Taylor
John Vandenberg
Katrina Varner
Dan Villeneuve
John Wambaugh
Andre Weaver
Erin Yost
Doug Young

**Other Participants:**

Paul Gilman, *Chair, BOSC Executive Committee*

**Contractor Support (ICF):**

Canden Byrd
Sophie Hearn
Kate Helmick