B O S C
Board of Scientific Counselors

REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY BOARD OF SCIENTIFIC COUNSELORS HUMAN HEALTH RISK ASSESSMENT (HHRA) SUBCOMMITTEE

RESPONSES TO CHARGE QUESTIONS

Human Health Risk Assessment Subcommittee

Katrina Waters, Ph.D. (Chair) *Pacific Northwest National Laboratory*	Chris Gennings, Ph.D. *Icahn School of Medicine at Mount Sinai*	Jane Rose, Ph.D. *Procter & Gamble Co.*
James Stevens, Ph.D. (Vice Chair) *Paradox Found LLC*	Dale Johnson, Pharm.D., Ph.D., DABT *University of California, Berkeley; University of Michigan; Emiliem Inc.*	Gina Solomon, M.D., MPH *Public Health Institute; University of California, San Francisco*
Anthony Bahinski, Ph.D., MBA, FAHA *GlaxoSmithKline*	Daland Juberg, Ph.D., ATS *Juberg Toxicology Consulting LLC*	Ponisseril Somasundaran, Ph.D., MS *Columbia University; Somasundaran Inc.*
Richard Becker, Ph.D., DABT *American Chemistry Council*	Juleen Lam, Ph.D., MHS, MS *California State University, East Bay*	Donna Vorhees, Sc.D. *Health Effects Institute; Boston University*
Juan Colberg, Ph.D. *Pfizer Inc. Worldwide Research and Development*	Timothy Malloy, J.D. *University of California, Los Angeles*	Clifford Weisel, Ph.D. *Rutgers University*
Richard Di Giulio, Ph.D., MS *Duke University*	Jennifer McPartland, Ph.D. *Environmental Defense Fund*	Mark Wiesner, Ph.D. *Duke University*

EPA Contact
Tom Tracy, Designated Federal Officer

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LIST OF ACRONYMS

BACKGROUND

The Human Health Risk Assessment (HHRA) National Research Program advances the scientific basis for risk assessments, including development of contemporary hazard identification and dose-response evaluations, and characterization of new data and science (such as those developed through the CSS program) for advancing to risk assessment practice.

HHRA develops a portfolio of fit-for-purpose assessment products that meet the expressed needs and priorities of customers, including EPA program offices and regions, states, and tribes. These assessment priorities have been formally received from Congress (e.g., criteria air pollutants) and Agency programs and regions (e.g., IRIS and PPRTV priorities), and, as assessment documents, are peer reviewed by other advisory committees, such as the Science Advisory Board (SAB), the SAB Clean Air Scientific Advisory Committee (CASAC), and the SAB Chemical Assessment Advisory Committee (CAAC). The focus of the BOSC CSS-HHRA Subcommittee review is the foundational research described in the StRAP document, which underpins HHRA's vision to advance the science and practice of risk assessment to support the EPA programs and regions, states, and tribes.

The HHRA StRAP document is now in internal EPA development/review and will be transmitted to the BOSC for review after the April 2019 Subcommittee meeting. During the April BOSC meeting, initial feedback is requested on the overall strategic direction of HHRA, based on materials provided at the meeting, including an overview of the program and posters/demonstrations showcasing the foci of planned research. The BOSC review will be guided by the HHRA Charge Questions listed below. The BOSC Subcommittee will complete its review of HHRA following transmittal of the StRAP, later this summer.

STRAP RESEARCH OBJECTIVES

Text

CHARGE QUESTIONS AND CONTEXT

The HHRA Subcommittee was charged with four questions as follows:

> Q.1: Does the research outlined for the 2019-2022 timeframe support HHRA's ability to deliver the range of assessments the Agency is requiring?
>
> Q.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.
>
> Q.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.

Q.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?

SUBCOMMITTEE RESPONSES TO CHARGE QUESTIONS

Introductory paragraph that highlights any overarching responses.

Based on HHRA presentations, posters, and demonstrations, the HHRA research areas and proposed outputs appear to align well with the vision of the program. The value of HHRA expertise and products to EPA partners and stakeholders is tangibly evident to the BOSC.

As described in the poster, *HHRA Science Assessment Translation and Support*, HHRA manages two of ORD's Technical Support Centers (TSCs): Superfund Human Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC). Through STSC, HHRA is able to provide critical technical support to regions, other federal agencies, and even international entities. For example, in response to a request from Region 2, HHRA provided technical assistance in developing relative potency factors, using expert driven-read across approaches, for chemicals of interest lacking toxicity values. The same poster also described how HHRA provides key technical support to program offices such as the Office of Water, Office of Air and Radiation, and Office of Chemical Safety and Pollution Prevention.

HHRA's commitment to educating agency partners and other stakeholders on the application of systematic review in environmental health is commendable and should be continued and further strengthened. Systematic review is a tool for increasing transparency, rigor, and consistency of chemical assessments and has been recommended by several National Research Council reports, *Science and Decisions (2009); Phthalates and Cumulative Risk (2008);* and *Review of EPA's Integrated Risk Information System (IRIS) Process (2014).* In recent years, HHRA has been at the forefront of developing and implementing systematic review methodology for chemical assessment. HHRA has established a "Community of Practice" for systematic review within EPA that has also been recently extended to other federal agencies. HHRA is also providing systematic review training to scientists in federal and state agencies. These engagements provide valuable opportunities for HHRA to build the environmental health systematic review community, and maintain a leadership position in advancing systematic review methods for chemical assessment.

Specific areas of strength as well as suggestions for the HHRA StRAP are described below.

Charge Question 1

Q.1. Does the research outlined for the 2019-2022 timeframe <u>support</u> HHRA's ability to deliver the range of assessments the Agency is requiring?

Feedback

- HHRA demonstrated impressive increased output and efficient use of time in generating work products, for instance by employing literature search capabilities that capitalize on recent advances in machine learning. The machine learning software employed prioritizes search results so that screeners review studies that are most likely to be most relevant to the study question first, and continually updates the prioritization order by learning as screeners review studies. During the

presentations, HHRA also highlighted potential interest in collaborations with external entities, such as IBM Watson, to further enhance and integrate machine-learning capabilities into its workflows. We encourage the continued use of machine learning to streamline the identification of relevant literature and data in systematic review to the greatest extent possible.

- HHRA research to advance approaches for the derivation of risk-specific doses for noncancer effects is impressive and directly responsive to two National Research Council reports, *Science and Decisions* (2009) and *Review of the IRIS Program* (2014). Specifically, HHRA is developing case examples using the APROBA methodology developed by the World Health Organization (WHO) International Program on Chemical Safety (IPCS)—a methodology for calculating probabilistic RfD estimates (see poster: *Quantitative Noncancer Risk: IPCS Approach to Uncertainty*). Furthermore, plans to integrate the APROBA methodology into the EPA's BMDS software in future versions will increase the accessibility and ease of use of this novel approach for the Agency as well as external users.
- Another strength of HHRA research efforts is the use of freely available software programs with data sharing capabilities such as SWIFT-Review and HAWC that can be used both by agency partners and external stakeholders for chemical assessment work, as well as the creation of open databases like HERO for literature searching, reference tracking and organization, and tagging. Use of free and open chemical assessment tools such as these increases the transparency, reproducibility, and efficient updating of HHRA assessments products and also increases their accessibility and utility to partners and stakeholders.
- Development of improved uncertainty methods is an important advance that will contribute to analysis of future issues dealing with multiple exposures and sensitive populations.
- The BOSC notes that HHRA has been developing and institutionalizing work flows that are problem formulation-driven and fit-for-purpose so that there is strong alignment of HHRA applied research projects with the specific decision contexts of the programs they serve. This will enable identification and selection of case-specific tools and methods that will help to optimize HHRA's investment of resources to achieve the applied research objectives in a timely manner.
- So far in fiscal year 2019, HHRA staff have reported over 4,000 hours of support, on a broad array of issues, to program and regional offices. The availability of concrete, on-demand, hands-on support from HHRA to agency partners is a strength and to be commended.

Charge Question 2

> Q.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.

Feedback

- While the HHRA research outputs appear relevant to the HHRA vision, specific research activities are not yet articulated. The committee anticipates that HHRA will clearly articulate the research activities that will be undertaken in its StRAP.
- During the in-person meeting, the committee repeatedly highlighted the importance of prioritizing and continuing research on chemical mixtures for both CSS and HHRA. Such research is critical to assessing real-world impacts of chemical exposures. The committee recommends that mixtures research and work on cumulative risk assessment be an explicit component of both research programs.

- The BOSC notes that the previous HHRA StRAP included objectives to evaluate mixtures, including chemical and non-chemical stressors, to support cumulative risk assessment. The 2016 report of the BOSC particularly commended these efforts. The presentations at this meeting did not clearly reflect that HHRA is continuing to prioritize research on methods that could apply to mixtures or cumulative exposure and toxicity assessments. The potential risk from what is known as the 'cocktail effect', caused by mixtures of chemicals at low levels, needs to be investigated and the risk to human health better understood. For example, the NAS recommended use of cumulative risk assessment for phthalates, but the poster presentations appeared to be evaluating phthalates individually. Moreover, the BOSC was advised that work on phthalates had been stopped despite clear guidance to pursue such analyses by the National Academies. At a minimum, the StRAP for HHRA (and other programs) needs to anticipate that such policy shifts will occur and explain how the agency will maximize the benefit of work completed to date.
- The HHRA StRAP should clearly specify what falls within and outside of its scope of work as it relates to risk assessment and the exposure and toxicity data that informs such assessments. This clarity will allow the BOSC to provide guidance better targeted to HHRA's charge. For example, HHRA's poster presentations focused more on toxicity than exposure. The 2016-2019 StRAP emphasizes exposure assessment with "Science Challenge 2" to [b]roaden exposure assessment technology with exposure factors for translation of exposure, bioavailability, and dose estimates (both human and ecological) to flexibly address different exposure scenarios." It would be helpful to clarify the extent to which exposure considerations are within the purview of the HHRA research program.
- The BOSC supports the integration of human health risk assessment with ecological assessment, but it will be important to describe in the StRAP how such integration will occur.
- HHRA has invested in educating and training agency partners and other stakeholders on the application of systematic review for chemical assessment. In the HHRA StRAP, the committee would like to see these efforts further developed in a way that clearly supports the HHRA vision. Specifically, we recommend that the StRAP include concrete examples of how training will be developed and deployed into the future.
- The BOSC commends the documentation of requests for technical assistance. HHRA should consider analyzing the requests that come in from the regional offices and other partners and stakeholders to identify areas of need in furtherance of science challenges specified in the 2016-2019 StRAP: (1) "Enhance data access and management systems to support transparency and efficiency" and (2) "Develop and apply effective methods for stakeholder engagement and risk assessment training to varied audiences." HHRA could then develop action plans in the StRAP to more systematically address the identified areas of need, which would ideally be summarized in an appendix to the StRAP.

Charge Question 3

> Q.3. HHRA has been collaborating with CSS on laying the foundation for future risk assessments. Please comment on the extent to which HHRA research and program deliverables are prepared to use novel data streams and tools, such as those from CSS, to advance the future of assessment science.

Feedback

- Overall, the BOSC was very impressed with the vision for coordinated development of products with CSS (e.g., RapidTox).

- HHRA's proposed Research Area 3, Emerging and Innovative Assessment Methodologies, includes three research outputs that are directly oriented around advancing the incorporation of NAMs into chemical assessment. The committee views such effort as a valuable and important component of HHRA's research agenda. Already, there are clear efforts by HHRA to integrate CSS products into the practice of chemical assessment as conveyed through posters, demos, and the presentation by the HHRA national program director. For example, the poster, *New Approach Methodologies in Human Health Risk Assessment,* illustrated how HHRA is exploring the use of three different types of NAMs—read across, transcriptomics, and high-throughput *in vitro* testing—in chemical assessment for purposes ranging from analogue selection to AOP development and BMD modeling of dose-response gene expression data.
- The decision context will inform the complexity of the analyses and the degree to which HHRA needs to depend on or utilize the variety of tools/approaches offered by CSS research (i.e., there is no requirement for HHRA to utilize or overlay its assessment sciences approaches on all available research initiatives currently developed or being developed by CSS).
- HHRA is making appropriate use of CSS tools (e.g., BMD software improvements using ToxCast data, which will be assessed for chemicals with good animal toxicology data and application of read-across methods, transcriptomics, and other tools to identify appropriate surrogate toxicity information for p,p-DDD at the Passaic River site). These efforts should be continued and expanded, with greater interaction among staff in the two programs. For example, CSS's virtual tissue research is ripe to test with antiandrogenic chemicals, which could be useful to HHRA's assessments of phthalates. Conversely, CSS could benefit by using some of the technology being successfully leveraged by HHRA, such as machine learning software, something that has apparently resulted in a 60% increase on productivity for selected HHRA activities.
- Acknowledging that HHRA is already taking steps to include use of NAMs into its chemical assessment work and research, the committee suggests that HHRA identify specific case studies that it will pursue to examine different applications of NAMs in chemical assessment. For example, HHRA could pursue case studies that showcase how NAMs may be used to build confidence in chemical assessments, the extent to which NAMs can or cannot be used as stand-alone for decision-making, and how NAMs may be employed in the assessment of chemical mixtures. A specific research activity discussed at the in-person meeting involved taking an existing set of PPRTV values and comparing such values with those derived solely using NAMs. In general, research and case study development around the use of NAMs in chemical assessment should explicitly include exploration of the application of CCS products. Case studies would help to build collaborations and lines of communication between HHRA and CSS.
- Using computational tools and approaches, such as those in Patlewicz et al, 2018 [https://www.sciencedirect.com/science/article/pii/S2468111318300689; high throughput exposure modelling (ExpoCast/SEEM) and the Threshold of Toxicological Concern to determine margins of safety) may provide sufficient scientific confidence for risk-based prioritization.
- Ideally, HHRA could base the design of assessments on a systems biology model (or models), such as AOPs or MOAs. Information from CSS data streams (e.g., high throughput, high content, biological activity profiling transcriptomics, high content phenotypic profiling, etc.) are anticipated to be most useful in understanding potential bioactivity associated with early or intermediate key events in systems biology models. Accordingly, PECO statements, where appropriate, could include hypothesized MOAs/AOPs to ensure such novel data streams and relevant mechanistic data (and modeled bioactivity results) play an appropriate role in causal analyses (e.g., biological plausibility, weight of evidence, etc.).

Commented [GS1]: This wasn't discussed at the meeting and seems to be a very specific recommendation. Should we keep or not?

- HHRA should, of course, look beyond CSS 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 assessments. Examples include NTP initiatives, models or methods developed by academics, other scientific experts and research institutions, etc.

Charge Question 4

Q.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?

Feedback

- The previous 2016-2019 HHRA StRAP included a research focus on epigenetic and other susceptibility factors in risk assessment. Specifically, it described "Science Challenge 8: to [e]xpand CRA [cumulative risk assessment] methods to advance "place-based" community risk characterizations, apportion multimedia exposures and risk to various receptors, incorporate multiple stressors, consider epigenetics and susceptibility, and support multi-criteria decision analysis and sustainability." The BOSC previously commended this area of research, and it remains important for improving the toxicity evaluations that support risk assessments , especially those involving children and other vulnerable subpopulations. An epigenomic risk assessment approach should be addressed by the new HHRA StRAP.
- Under the funding Programme, Horizon 2020, the EU has started to address the issue of mixtures. As reported by Bopp et al (Environment International 120 (2018) 544-562), there are several projects working on "developing methodologies to better assess chemical mixtures, by generating and making available internal and external exposure data, developing models for exposure assessment, developing tools for in silico and in vitro effect assessment". Projects like EDC-MixRisk, EuroMix, EUToxRisk, HBM4EU and SOLUTIONS are already working on this and their model could be a way for the EPA to address developing solutions to this issue under reduced resources and funding. The BOSC suggestion is for the EPA to evaluate the feasibility of collaborating with the EU on this project.
- Progress to date on developing systematic review methods is impressive, and the BOSC strongly supports continuation of this work with strong processes for assessing risk of bias. HHRA should focus some effort on the development of improved methods to incorporate mechanistic studies into systematic reviews (including grading such studies at the evidence integration phase).
- CSS and other ORD programs are evaluating some important emerging issues (e.g., 3-D printers, algal blooms, microplastics) that could benefit from HHRA research that is conducted in coordinated fashion with the other efforts, if resources permit.
- Important to public health is inter-agency coordination (CPSC, FDA, EPA) focused on risk evaluation of compounds that fall across intra-agency purviews. For example, phthalates are present in consumer products, enteric coating in oral medication, and cosmetics. HHRA should work with other agencies to coordinate assessments based on human relevant exposure and risk estimates. Perhaps biomonitoring data (e.g., NHANES) can be used to demonstrate population level exposure estimates to single compounds and mixtures. Further, the HHRA should work with international groups focusing on grouping chemicals in hazard and risk assessments (e.g., policies on EDCs in the EU; the mixtures mandate in the HBM4EU).

CONCLUSIONS

Add brief text that summarizes main findings.

APPENDIX A: MEETING AGENDA

APPENDIX B: MATERIALS

Material Provided in Advance of the Meeting

Materials to Support the Charge Questions

- Bulleted list

Informational Materials

- Bulleted list

Additional Material Provided During the Meeting

- Bulleted list