B O S C
Board of Scientific Counselors

REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY BOARD OF SCIENTIFIC COUNSELORS CHEMICAL SAFETY FOR SUSTAINABILITY (CSS) SUBCOMMITTEE

RESPONSES TO CHARGE QUESTIONS

Chemical Safety for Sustainability Subcommittee

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April ?, 2019

A Federal Advisory Committee for the U.S. Environmental Protection Agency's Office of Research and Development

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CHARGE QUESTIONS AND CONTEXT

The CSS/HHRA Subcommittee was charged with five questions as follows:

> Q.1a: Does the research outlined for the 2019–2022 timeframe support the relevant Agency priorities as described in the EPA and ORD Strategic Plans?
>
> Q.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?
>
> Q.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.
>
> Q.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?
>
> Q.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?

SUBCOMMITTEE RESPONSES TO CHARGE QUESTIONS

The 2019-2022 CSS StRAP was developed through multiple interactions, meetings, workshops, and consultations between ORD scientists, EPA partners, and external stakeholders. The overarching goals of the CSS program are to compile and formulate existing and new data to manage chemical risks in order to protect human health and the environment. This has been and continues to be focused on the

following goals and outputs: creating, enhancing, and maintaining a robust chemical safety informatics infrastructure to support decision makers at all levels; creating relevant data via high throughput hazard and exposure methodology to fill data gaps that would otherwise make decisions more difficult; incorporating and establishing a complex systems science approach to enhance interpretations and decision-making at all levels of data development and usage; approaches to extrapolate and extend the applicability of multiple sources and types of data among chemicals, between species, at different life stages, and biological levels of organization such as organelle, cells, tissues, organs, organ systems, organisms, populations, communities, ecosystems, and the biosphere; and the enhancement of chemical safety evaluations to include consideration of sensitive populations and life stages. During the 2019-2022 timeframe, CSS will concentrate on the development, demonstration, delivery, and application of CSS data, tools, models, and the informatics infrastructure through partner and stakeholder engagement to meet both immediate and high-priority needs.

[need more here]

Charge Question 1a

> Q.1a. Does the research outlined for the 2019-2022 timeframe support the relevant Agency priorities as described in the EPA and ORD Strategic Plans?

Narrative

The EPA Agency Strategic Plan has shifted toward three central goals: "Core Mission, Cooperative Federalism, and Rule of Law and Process." Specifically, EPA plans to: "(1) refocus the agency back to its core mission of protecting human health and the environment; (2) restore power to the states through cooperative federalism; and (3) lead the agency through improved processes and adhere to the rule of law." In addition, the safety of chemicals in the marketplace is prioritized as part of the implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

ORD's overarching strategic metric is stated in its 2019-2022 Strategic Plan as: "By September 30, 2022, ORD will increase the number of research products meeting customer needs." ORD also lays out three Goals that parallel Agency goals in its Strategic Plan:

> Goal 1: Enhancing Environmental Science and Technology: ORD will work with its partners to identify high priority research needs and develop the research tools necessary to inform environmental decision-making at the local, state, regional, national and international level. ORD will refine its research efforts and finalize the 2019-2022 StRAPs based on feedback from decision-makers.
>
> Goal 2: Cooperative Federalism - Informing Federal, State, Tribal and Local Environmental Decision-making: an overarching approach to strengthen relationships with states has been adopted, outlining engagement activities and opportunities to inform decision-making.
>
> Goal 3: Enhancing and Sustaining a Strong ORD Workforce and Workplace: an ORD Workforce Strategy has been developed.

One of the EPA strategic plan goals is to "ensure compliance with the law by providing consistency and certainty for the regulated community and clarify the impact of proposed actions on human health, the environment and the economy to provide a clear path and timeline for entities to achieve compliance." The revised StRAP, however, is calling for the former Sustainable Chemistry research area to be "refined

and renamed Chemical Safety Analytics (CSA). This change reflects a reduced emphasis on sustainable chemistry." Although, the change addresses the high-priority need for better toxicity assessment methods, it sacrifices another aspect that is important for the regulated community, which is identification of safer chemical alternatives. Although efforts to identify safer alternatives could be achieved via collaborations between the private and academic sector, ORD is in the unique position to drive the research needed to identify safer chemicals. This could be achieved with a minimum ORD budget/resources commitment by collaborating with a scientific consortium, something that has been used globally.

The EPA and ORD priorities include a broader focus than the current principal focus of CSS. It appears that the CSS is currently focused on producing tools for the TSCA program and the pesticide program. These are both important, but given the EPA and ORD priority of cooperative federalism, it is important for CSS not to lose sight of important priorities associated with the regions and states, as well as with other program offices at EPA, most notably OLEM. These entities are often dealing with complex mixtures of chemicals in the environment, degradation products of chemicals, and chemicals that may not be currently manufactured, but have been released to the environment. The BOSC did not see much as much effort as may be warranted in these important areas.

Strengths

- The state-of-the-art science being conducted to understand exposures and toxicological effects to humans and ecosystems provides the necessary underpinnings to meet the core EPA Mission of providing clean air, land, and water, and ensuring chemical safety.
- Interactions with EPA Program and Regional Offices enable them to carry out their missions when issues related to contaminants in the environment arise.
- There is strong vision and breadth in pulling together informatics, methods and analytical tools to create an integrated system for use in prediction and screening for chemical evaluation
- Investments made throughout the last 10–year period are coming to fruition, and current efforts demonstrate vision for what is needed in the future.
- Tools and methodologies being developed are relevant, and are being applied to meet Agency priorities as identified by Program Offices.
- Strategic outputs described for the research areas have incorporated more agency mission products than in previous years, documenting the greater role the CSS has had in supporting the Agency's mission.
- The BOSC commends the research effort focused on chemicals that are difficult to test (e.g., volatile or insoluble in DMSO), as these chemicals could otherwise be unaddressed by the emerging testing methods.
- CSS has developed expertise in multiple scientific research areas to evaluate physical, chemical and biological transformation of chemicals in the environment and endogenous metabolism that can contribute to addressing uncertainties in estimating or predicting exposure and dosimetry. CSS capability includes state of the art scientific laboratory and modeling capabilities.

Suggestions

- It may be helpful to more explicitly tie research activities to the problem formulation / decision contexts of the program offices (TSCA new chemicals, TSCA inventory prioritization, TSCA tox data gap filling, etc.)
- ORD could benefit from a more robust computer/computational modeling program, something critical for the development and maintenance of the tools currently being developed.

- Consider approaches to testing and assessment that use biological activity exposure ratio (e.g. integrate exposure with tox/bioactivity).

Recommendations

The Subcommittee offers these recommendations to capitalize on further align the StRAP with the EPA and ORD strategic plans:

Recommendation 1a.1: A de-emphasis on early stage LCA and sustainable chemistry may impact the ability to evaluate emerging chemicals and materials, and to compare alternatives. However, the current research effort is developing many of the elements of early stage LCA, including chemical screening and ecosystem impact tools. We recommend that the effort to include early stage LCA as a decision-making tool along with on-going work should not be de-emphasized as it would appear to be both needed and cost effective.

Recommendation 1a.2: Toxicological evaluation of chemical mixtures, based on common chemical co-exposure, should have a higher priority.- This should augment the current focus on individual chemical species or chemical groups so that future efforts include exposures and use of materials that include complex mixtures of chemicals. The StRAP should present better articulation and inclusion of mixtures in case studies and strategic outputs.

Charge Question 1b

> Q.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?

Narrative

CSS has made a considerable effort to identify needs of program offices, regional offices, states, and tribes and develop tools that are readily available for use, along with CSS personnel availability to help partners and stakeholders with their use. That said, there are challenges with the interaction with the states and tribal groups due to the large range of needs and scientific expertise among those entities, and the StRAP did not reflect as much outreach to some entities as others. For example, a survey through ECOS is not necessarily likely to surface the many ways that CSS products could help states to carry out their work. The StRAP document and presentation outlines some of the approaches being used. CSS has made strides in developing and making available tools that facilitate the Agency in addressing core goals.

In the draft StRAP, CSS explains that a plan was developed to elicit the research needs of its partners, directly following from goals outlined in EPA's overarching Strategic Plan, and to outline a plan for meeting those needs. As defined in the StRAP, CSS's partners are EPA program and regional offices, states, and tribes (including organizations and subsidiaries thereof), although CSS National Program Director, Dr. Jeff Frithsen, explained to the BOSC that the needs of EPA program offices and regions take priority in defining CSS research, despite the Agency priority of cooperative federalism.

Since mid-2017, CSS has worked to identify the research needs of its partners by "conducting topical workshops, briefing partners on CSS StRAP development, conducting regularly scheduled consultations, collaborating with partners on programmatic strategies and plans, and providing opportunities for partners to review the CSS StRAP at different stages of development." Appendix 1, "Partner and stakeholder needs and CSS strategic outputs" summarizes the "highest priority needs" of all partners, while Appendix 2, "Partner and stakeholder engagements to inform the CSS StRAP development" and Appendix 3, "State needs as conveyed to EPA by the Environmental Council of States (ECOS)," are meant to capture various interactions and solicitations used by ORD to identify partner needs.

Strengths

- The StRAP provides evidence that CSS sought to identify and prioritize the research needs of its partners. They did so through an extensive series of workshops, meetings, and other formal and informal collaborations. Importantly, the proposed research outlined in the StRAP is generally designed to be responsive to the partner research needs.
- During the in-person BOSC meeting, representatives of various program offices (OPPT, OPP, OW, OLEM, OCSP) discussed their programmatic needs; the ways in which they are, or envision, using CSS products to fulfill their duties; and where collaboration between program offices and CSS is occurring. Dr. Fristhen also identified ongoing dialogue with regional science liaisons and Superfund Technical Support Centers. These presentations highlight the constructive and ongoing engagement between CSS and EPA program offices. However, unlike at prior meetings of the BOSC, no regional office representatives were present at the meeting, making it appear as if the regions and states have been de-prioritized compared to prior StRAPs.
- EPA's Regional Applied Research Effort (RARE) represents an agency program to engage regional offices in collaborative research with ORD experts. The project "Application of 21st century bioanalytical tools to identify sources and effects of bioactive contaminants associated with select municipal wastewater discharges to the South Platte and Colorado River watersheds" is an especially exciting RARE collaboration between CSS and EPA region 8. Some of the poster presentations highlighted other important collaborations to ensure the effective use of CSS research by EPA regions (e.g., RapidTox). This effort illustrates the value of strong partnerships with regions and states.

Suggestions

- The outreach efforts to partners and stakeholders could be more fully described. In the meeting discussion, it became clear that the CSS program had conducted more outreach than was described in the StRAP and appendices. While Appendices 1, 2, and 3 document important steps taken to ascertain research needs of CSS's partners, several important aspects of the engagement process and its outcome remain opaque in the StRAP. For example, the StRAP lacks discussion of how regional partner needs were identified beyond the fact that meetings, workshops, and collaborations occurred. How were partner representatives identified and recruited to ensure that relevant voices were heard? Were research needs solicited from all EPA program offices and regions, states, and tribes? How exactly were research needs elicited? For example, it is not entirely clear whether the three meetings with tribes (Appendix 2) provided tribes an opportunity to identify research needs in addition to hearing CSS summarize progress being made on the development of the StRAP. And, finally, what criteria did CSS use to classify research needs as "highest priority"?
- There are many references to stakeholders in the StRAP. For example, the StRAP makes reference to developing a research agenda that aims to solve "the problems encountered by

Agency partners and stakeholders" and that the StRAP "evolved through a series of meetings, workshops, and consultations with Agency partners, ORD scientists, and interactions with external stakeholders." However, the StRAP document does not describe who these specific stakeholders are nor what types and how interactions with stakeholders informed the direction of the StRAP. To the extent, the StRAP was designed to responsive to stakeholder needs in addition to partner needs, it is important that these stakeholders be defined and more discussion provided of how their needs were identified and used to inform the StRAP.

- The CSS-HHRA partner relationship is unique and especially valuable for increasing use of NAMs in risk assessment. Among other critical roles, HHRA serves an important intermediary for evaluating, piloting, and advancing the use of NAMs in risk assessment and translating such learnings and experience to risk assessment practitioners on the ground that include agency partners. CSS should include HHRA in its partner outreach efforts to identify opportunities for advancing the use of NAMs in risk assessment. For example, HHRA could be very helpful in evaluating/validating the outcomes of NAMs toward building confidence in their use in risk assessment, including where they can appropriately be used to reduce or replace the use of animals. Similarly, CSS could engage with HHRA to identify gaps in the data available for current risk assessments that might be informed by NAM outputs.
- OCSPP is CSS's primary partner, but CSS products and tools are of immense value and relevance to all agency partners looking for solutions related to chemical assessment and decision-making. Ideally, CSS would pursue research in a manner that serves the needs of all of its partners and frame CSS products in a way that conveys their utility to multiple partners. CSS could specify how each of its products can be directed toward answering specific partner questions and helping to provide solutions for specific partner needs.
- Ongoing education and training, ideally involving beta testing and piloting of CSS products, is essential to encouraging confidence in the products and their adoption for use by CSS partners and stakeholders, such as industry, academia, NGOs, and the public. Widespread use of CSS products will lead to constructive input that, in turn, will lead to more scientifically robust and useful products over time.
- Resources permitting, CSS could consider developing an education and training plan, including pilot projects with a range of partners and stakeholders within and outside EPA. Education could come in many forms, such as recorded web demo videos, user guides, training modules, and partnering arrangements with professional societies. Training could be enhanced with development of chemical-specific AOP case studies. In addition, CSS's work on PFAS may provide a good opportunity to educate, train, and pilot CSS products with partners. In all educational efforts, it will be important for CSS to understand where partners are with respect to their own expertise and research needs to encourage rapid adoption of CSS products.
- CSS could explore opportunities to work with relevant program offices to use the high throughput new exposure modeling tools to identify potential emerging contaminants.
- CSS could work with the program offices to develop a set of principles and approaches for establishing scientific confidence for the methods and new datastreams to meet the different program office decision contexts. These scientific confidence principles and approaches should be scientifically robust and yet sufficiently flexible to enable application across tools, models and methods and decision contexts.
- The CSS program should develop more specific measures for integrating input from its partners as well as other potential users of its products throughout the research project life cycle. These measures should include more proactive interaction during the problem formulation and research design stage with stakeholders and partners to align needs and anticipate issues. Also,

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such measures may include more extensive beta testing of research products with potential users prior to their broader release. Beta testing may be an inventive for researchers to get involved in testing new tools or modifications to existing tools by gaining early access. This also encourages stakeholder feedback at early stages of tool development to ensure that these products are meeting the needs of its ultimate users.

Recommendations

The Subcommittee offers these four recommendations to capitalize on engagement with CSS partners to identify priority research needs.

Recommendation 1b.1: For *future* StRAPs, develop 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. The plan should include 1) how partners will be engaged, 2) how input from partners will be solicited, and 3) how identified needs will be prioritized for inclusion in the CSS StRAP. CSS should seek guidance from partners as to how they would like to be included in the research planning process and then tailor the plan as needed to specific partner groups. With this recommendation, the BOSC does not intend to impose an onerous process on CSS that unnecessarily detracts from its excellent research. Instead, CSS should define an efficient process to allow for the effective elicitation of partner needs while also being transparent to the BOSC and other reviewers.

Recommendation 1b.2: For the *current* StRAP, develop a partner engagement plan as described in Recommendation 1b.1, solely for the purpose of soliciting feedback from partners regarding *implementation* of the CSS StRAP.

Recommendation 1b.3: For the *current* StRAP, identify a set of activities that CSS will pursue to advance partner education, training, and piloting of CSS products.

- Coordinate with HHRA to support this effort; HHRA has long-standing relationships with EPA regional offices and states through its superfund technical support networks and could assist with training and educating practitioners on CSS products.
- Continue and strive to expand on the RARE effort and report to the BOSC and CSS partners on the results, including achievements and lessons learned for CSS product transfer to Region 8 and other partners.
- Take advantage of CSS's work on PFAS as an opportunity to educate and train partners, including piloting of CSS products.

Recommendation 1b.4: For the *current* StRAP, develop a set of activities to pursue regarding broad stakeholder outreach and engagement around CSS research and products with the goal of building confidence in CSS products. This confidence will, in turn, promote the acceptance and use of the products in risk assessment and regulatory decision-making for the protection of human health and the environment.

Recommendation 1b.5: The StRAP should include discussion of how the work in CSS relates to other research activities at ORD, and how the research agenda was informed by the needs of these other research programs, particularly the HHRA program activities.

Charge Question 1c

Q.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.

Narrative

The BOSC was impressed with the clarity and coherence of the strategic vision of the program. The research as outlined and the proposed outputs in the CSS StRAP 2019-2022 clearly define the desired research vision of the CSS program. The informatics and database developments over the last 3 years along with the continued enhancement and updating are exceptional and will provide detailed and accurate information sources for partners, stakeholders, and the public for chemical safety evaluation. These programs will clearly be the international model for chemical resource data to protect human health and the environment.

The current StRAP emphasizes modeling and computational approaches and appears to de-emphasize measurement approaches. For example, the Rapid Exposure Modeling and Dosimetry (REMD) research area only includes a brief mention of analytical chemistry research areas (environmental monitoring, non-targeted testing), and the document overall contains greater emphasis on computational toxicology than on chemical testing approaches (high-throughput, medium-throughput, and high-content). Although the progress on computational approaches is impressive, the BOSC believes that the analytical chemistry and biological activity testing activities at CSS need more emphasis in the StRAP.

The StRAP does not contain much specific discussion of work going on related to susceptible populations, including children, workers, and affected communities. Children are mentioned only under the heading "Integration Among Research Programs" on p. 25 of the StRAP. The paragraph related to susceptible subpopulations should be described more clearly and included under a more appropriate heading, in order to increase clarity in the document.

The research area on Emerging Materials and Technology is currently rather thin, containing only two strategic outputs, and focusing only on nanomaterials. This area could easily be enhanced to incorporate additional emerging issues. For example, the research into 3-D printing has important health relevance, and work on microplastics would fit well into this research area.

The BOSC was impressed with the work presented on Adverse Outcome Pathways (AOPs) in the poster session, but much of that work is not reflected in the StRAP, causing the committee to wonder whether that work is being deemphasized. For example, work to obtain formalin-fixed samples from prior toxicology studies to evaluate early biological markers, and work on mRNA markers is important for helping to establish and validate AOPs and to increase confidence in their use, but it is not described in the StRAP.

Strengths

- The StRAP is very clear, readable, and strategic. It provides a coherent structure for the research agenda of the program.

- The three-year objectives of the program are measurable and potentially feasible in the time frame provided.
- The StRAP describes a research agenda that is ambitious and relevant to near-term policy decisions.
- The alternative, non-vertebrate chemical testing program, such as the virtual tissue program and high-throughput testing is well-known and supported by all international regulatory groups.
- The StRAP describes a commitment to ensuring transparency and collaborating with partners and stakeholders at various stages of the product development and implementation process. One such example of this approach is the collaborative process by which Computational Toxicology Chemicals (CompTox) Chemicals Dashboard has been developed and rolled out to users.

Suggestions

- The StRAP should clarify how this research agenda relates to other ongoing research by Federal agencies, such as the National Toxicology Program (NTP) on related issues, and how CSS is partnering with NTP to advance NAMs.
- Consider adding more detail to the StRAP on important ongoing work on emerging materials and technologies and on Adverse Outcome Pathways (AOPs).
- A fuller discussion in the StRAP of work to address sensitive or highly exposed subpopulations, such as children, workers, affected communities, and others, would be a helpful addition.
- It is unclear what research efforts will be focused on complex substances, UVCBs, and mixtures. Perhaps a needs assessment discussion with relevant program offices is warranted, but the BOSC would like to see some discussion of this issue in the StRAP.
- It is likely that not all tools, models, and the informatics infrastructures contained in the current StRAP goals can be completely finished and established during the 2019-2022 timeframe. Accordingly, there should be milestones in implementation for all products.
- One of these milestones would be to enhance AOPs into a quantitative and robust systems biology network/infrastructure where major environmental safety issues and new testing strategies can be covered by specific AOPs. As an example, with NAMs including virtual tissue models, specific quantitative AOPs should be established for the assay model itself. This would allow the quantification of key events that would serve as biomarkers which would then provide a level of evidence and reduce the uncertainty of the model screening output.
- Another suggested priority would be to enhance the capability of predicting internal exposure from environmental chemical exposure in different species. This could be done by coupling an *in vitro*/*in vivo* extrapolation (IVIVE) with several data generating models, including those where complex mixtures are screened. This could then eventually become a standard part of the AOP Knowledgebase informatics infrastructure and also enhance the ECOTox Knowledgebase.

Recommendations

The Subcommittee offers these three recommendations to more clearly and coherently describe the research agenda of CSS in the StRAP.

Recommendation 1c.1: Biological activity testing and analytical chemistry efforts in the CSS research portfolio needs to be more clearly described in the StRAP.

Recommendation 1c.2: The StRAP should include discussion of work in CSS that is relevant to susceptible subpopulations, including early life stages, and those with underlying sensitivities.

Charge Question 1d

Q.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?

Narrative

While ORD is positioned to assist EPA programs with their research initiatives, especially those that fall across multiple programs (e.g., focus on AOPs), it is also in a unique position to take a broader research view for protecting human health and the environment. The ORD clients are focused on their own initiatives and mandates – without adequate resources to address broader needs. ORD has the opportunity to "see the forest for the trees". For example, the Office of Pesticides is mandated to conduct cumulative risk assessment for groups of pesticides with similar modes of action. Such groupings are generally not based on human relevant exposures, but on individual chemicals or classes. Evidenced by pesticide use patterns across the growing seasons and from human biomonitoring data, humans are exposed to pesticides from multiple chemical classes.

Much of the focus of the CSS is towards single chemical evaluations (CompTox, AOPs) which are important and relevant to TSCA. However, ORD should also include the human relevant step of consideration of mixtures. This may be in the evaluation of constructed mixtures based on, for example, NHANES-based typical concentrations across chemical classes. Such a constructed mixture could be used in a QC step to evaluate the AOP framework in constructing PODs when exposure is to mixtures.
It would be useful to extend the AOP approach being used for mixtures for ecological health (e.g., Duluth Great Lakes Study; poster entitled Adverse Outcome Pathways and their Application I) to human health. In other words, do the same thing in a case study using biomonitoring studies and human health.

ORD should add biomonitoring equivalent values, when available, on the CompTox for readily available guideline values based on human biomonitoring concentrations. This will provide an opportunity for epidemiologists to access regulatory values relevant to their biomonitoring data.
Multiple stressors may also include non-chemical stressors.

The data supporting CompTox seems to be largely from in vitro and in vivo data. There are publically available human health and exposure data that could be incorporated. One example is the NHANES database – which is limited to a cross-sectional design. A valuable impending source is the CHEAR (Child Health Exposure Assessment Resource) data repository, the NIEHS-funded network of a national exposure assessment laboratory network, including epidemiologic data provided by study principal investigators and targeted environmental chemical panels. Importantly, many of the CHEAR studies include metabolomics data on study samples (from maternal and child samples).

The EAM theme should be expanded to include nano-plastics and 3-D printer byproducts.

Strengths

- Work on sources of exposure is important and demonstrates multiple sources of exposure for many chemicals.

- The dosimetry between in vitro and in vivo concentrations is very important and relevant to risk assessment.
- The research on PFAS chemicals provides an opportunity to consider applicability across chemical groupings and mixtures.
- There is great evidence on the cross-research collaboration between ORD groups/Projects for the successful delivery of NAMs. Current research seems to be aligned and moving forward.
- Regarding method validation/accuracy, ORD has taken steps to approach other global regulatory agencies to collect input and share data

Suggestions

- The ISI needs greater support to accommodate the need for computational tools that need to be consistently updated and reviewed as new data become available. Models cannot be static. The efficiency of the process would be improved with machine learning and AI.
- PFAS are clearly important; but they should not be emphasized to the point of not collecting data on other classes of chemicals.
- It could be that regulatory policies are not protective enough. So limiting consideration of mixtures only using groupings based on assumption of additivity (e.g., based on FQPA) is problematic.
- Consider using HTTK /IVIVE to develop biomonitoring equivalents: the concentration in human blood / urine that correspond to the PODs, PPRTVs. RfDs etc.
- The integration of AOPs with computer models of biological systems should be explored with the goal of developing quantitative models that include toxicokinetics and dynamic range of responses, dose-dependent transitions (e.g., tipping points from one key event to the next).
- The NAM approaches need to address the consideration of variability and uncertainties in in vivo data/ guideline studies (uterotrophic assay) allowing for a better understanding of the guideline data and identifying chemicals with a high quality response.
- Suggest ORD CSS work with OCSPP to evaluate ways to improve methods, models, scientific approaches in EPA's new chemicals program (EpiSuite was noted as having many issues). To include an evaluation of the CSS pre-prioritization proof of concept methods that may be applied in the new chemicals program and TSCA Section 4 (chemical testing), such as GenRA, threshold of toxicological concern, etc.

Recommendations

The Subcommittee offers the following recommendations to invest in other critical emerging environmental needs or fields of expertise or new research methods.

Recommendation 1d.1: High throughput testing should include mixtures of chemicals identified from biomonitoring studies, and other health- and ecologically-relevant mixtures.

Recommendation 1d.2: ORD should ensure that there is sufficient IT support for computational prediction tools and the staff expertise needed to support the shift from experimentation to computational/AI prediction approaches to address the EPA/ORD mandate.

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Charge Question 1e

Q.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?

Narrative

The CSS program appears committed to responding to the evolving needs of its partners and stakeholders through innovative research and the development of models, tools and other products to address existing and emerging environmental problems. As discussed above with respect to the prior charge questions, the research products play a critical role in enabling the Agency to meet its statutory obligations and strategic goals. However, creation of the research products is only one aspect of innovation; the products are only useful if adopted and appropriately implemented by the intended end-users. The CSS StRAP indicates that the program seeks input from its partners through a range of methods, including planned partner engagement at points during the research process and evaluation of the usefulness and effectiveness of the research products. However, the nature and scope of those activities are not described in detail within the StRAP.

The program rightly recognizes that its efforts are bounded by resource constraints and that the knowledge generation and innovation required exceeds the capacity of one program. It uses a variety of strategies to foster innovation relevant to its research priorities, including extramural activities that leverage the resources of other government programs, academic institutions, non-governmental entities and business. Examples include extramural grants such as the EPA's Science to Achieve Results (STAR) grant program, the Regional Applied Research Effort (RARE), innovation challenges, and interagency and international collaboration and outreach. These strategies and others like them are not costless; the value they bring to the program must be balanced against the opportunity costs they present. It is also unclear the extent to which funds will continue to be available to support such opportunities in the future.

Strengths

- The program appears to recognize that adoption and use of its research products are strongly linked with social, institutional and other factors aside from the scientific and technical benefits of the products. For example, planned research highlights for the adverse outcomes pathways (AOP) project includes identifying and implementing solutions to social, institutional, and IT barriers to AOP development and use.
- The STAR grant program and cooperative agreements have been key drivers of innovation. STAR grants in particular enhance and supplement the program's in-house research while building capacity and collaborations among academic scientists and engineers. As an example, the Organotypic Culture Methods (OCM) Centers represent a collaboration across six different universities that focuses on developing alternative test methods using physical and computational models of biological tissues. This active collaboration is contributing to scientific innovations through the development of novel toxicity screening tools. However, it appears that the program (and the Agency more generally) has made less use of STAR grants and cooperative agreements more recently.

Suggestions

- The development and use of AOP frameworks has been rapidly increasing in recent years. However, there remains a need to incentivize the posting of AOPs in shared database sites, such as AOPWiki, to increase accessibility, uptake, and use of models. The CSS program should consider incentivizing such contributions through simplified formatting requirements. Ensuring that databases are easy to use and require minimal time and effort will encourage greater participation among the researcher community.
- The CSS program should consider sponsoring and participating in a continuing workshop or colloquium series with one or more academic partners or professional/scientific societies focusing upon priority research topics. As an example, the Food and Drug Administration (FDA) has paired with the Society of Toxicology (SOT) since 2014 to present regular colloquia regarding innovative work in toxicological science relevant to the work of the FDA. A similar series featuring a partnership between the EPA and an external organization could greatly enhance the capacity of scientists and engineers within and outside the program, generate new collaborations, and drive novel scientific innovations.
- Building capacity and an informed public begins with education at all levels, from K-12 through graduate-level training. If feasible, the CSS program should consider cost-effective efforts to incentivize and assist in the development of appropriate curriculum relating to the areas covered by program research topics. Efforts could include development of curriculum and case studies by the program or program grantees as well as collaboration with educational institutions, professional societies and accreditation bodies. As an example, EPA's Office of Land and Emergency Management (OLEM) has developed environmental education materials geared at teaching both children and adults about the environment and issues such as Superfund sites. Resources include learning activities, environmental cleanup videos, and collaboration opportunities with EPA scientists.
- The CSS program should consider offering additional training in science communication to the CSS staff for preparation of materials or when interacting with the public regarding its scientific discoveries or sharing mission objectives related to the goals of protecting environmental and ecological health.

Recommendations

The Subcommittee offers these two recommendations to capitalize on specific ideas for innovation and market-based approaches that the program could use to advance solutions to existing and emerging environmental problems.

Recommendation 1e.1: The CSS program should strategically seek out opportunities to expand and increase the use of grant programs such as the STAR and the Small Business Innovation Research (SBIR) programs to drive research and innovation. These programs allow the program to leverage external funds by collaborating with other agencies and other external partners.

Recommendation 1e.2: The CSS program should consider developing an integrated suite of challenge/prize and recognition programs for partners and stakeholders who may invest in or use research products being developed by the program. In particular, it may be helpful to allocate resources for such programs for *each* of the research areas to fund necessary R&D that does fall within the stated expertise areas of the agency. This suite could build upon the experience gained through existing and prior programs. For example, the Transform Toxicity Challenge asked scientists to develop techniques to rework existing HTS assays to incorporate metabolism of chemicals. Likewise, recognition programs provide incentives and affirmation to entities whose research and activities complement those of the program. Challenge and awards programs offering modest awards and

recognition for graduate and post-graduate students should also be considered across each of the research areas.

SUMMARY LIST OF RECOMMENDATIONS

Add just the list of recommendations, if this is helpful.

CONCLUSIONS

The program has a variety of measures in place that support the creation and adoption of innovative tools and methods that are central to the Agency's mission. These measures could be enhanced by considering strategic expansions in scope or use. The research as outlined and the proposed outputs in the CSS StRAP 2019-2022 clearly define the desired research vision of the CSS program. With the continual partner/ stakeholder inputs and collaborations and top-level science at CSS, the program is certainly on track to advance the management of chemical risks in order to protect human health and the environment.

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