B O S C
Board of Scientific Counselors

REVIEW OF U.S. EPA OFFICE OF RESEARCH AND DEVELOPMENT'S RESEARCH PROGRAMS

Draft

BOSC Chemical Safety for Sustainability Subcommittee

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LIST OF ACRONYMS

AOP	Adverse Outcome Pathway
AOP-DD	Adverse Outcome Pathway Discovery and Development
BOSC	Board of Scientific Counselors
CAS	Chemical Abstract Service
CHAD	Consolidated Human Activity Database
CHEAR	Child Health Exposure Assessment Resource
CNT	Carbon Nanotubes
CPCat	Chemical and Product Categories
CSS	Chemical Safety for Sustainability
CSSP	Complex Systems Science Program
D&E	Demonstration and Evaluation
ECHO	Environmental Influences on Child Health Outcomes
EcoMod	Ecological Modeling
ECOTOX	ECOTOXicology Knowledgebase
EPA	Environmental Protection Agency
FACA	Federal Advisory Committee Act
FTE	full-time equivalent
HHRA	Human Health Risk Assessment
HTS	High Throughput Screening
HTT	High Throughput Toxicology
LCA	Life Cycle Analytics
LC-HEM	Life Cycle-Human Exposure Modeling
MIE	Molecular Initiating Event
MOA	Mode of Action
NIEHS	National Institute for Environmental Health Sciences
NIH	National Institutes of Health
OECD	Organization for Economic Cooperation and Development
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
PBPK	Physiologically Based Pharmacokinetics
RED	Rapid Exposure and Dosimetry
RFA	Request for Application
SeqAPASS	Sequence Alignment to Predict Across-Species Susceptibility
SDS	Sodium Dodecyl Sulfate
SHEDS	Stochastic Human Exposure and Dose Simulation
STAR	Science to Achieve Results
StRAP	Strategic Research Action Plan
SustChem	Sustainable Chemistry
TKTD	Toxicokinetic-Toxicodynamic
ToxCast	Toxicity Forecaster
TRI	Toxic Release Inventory
VTM	Virtual Tissue Matrix

BACKGROUND

The CSS and Human Health Risk Assessment (HHRA) Subcommittee of EPA's Board of Scientific Counselors (BOSC) conducted its second annual review at the EPA's Research Triangle Park Main Campus in Research Triangle Park, North Carolina on November 16-18, 2016. The following is the list of Subcommittee members who participated in the meeting:

- Ponisseril Somasundaran, Ph.D., Subcommittee Chair, LVD Krumb Professor and Director, Langmuir Center for Colloids and Interfaces, Columbia University
- Gina Solomon, M.D., M.P.H., Subcommittee Vice-chair, Deputy Secretary for Science and Health, California Environmental Protection Agency; Clinical Professor of Medicine, University of California San Francisco
- Paloma Beamer, Ph.D., Associate Professor, College of Public Health, University of Arizona
- Chris Gennings, Ph.D., Research Professor, Icahn School of Medicine at Mount Sinai
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- Rebecca Klaper, Ph.D., Professor, School of Freshwater Sciences, University of Wisconsin-Milwaukee
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- Donna Vorhees, Sc.D., Principal Investigator and Adjunct Assistant Professor, The Science Collaborative and Boston University School of Public Health
- Katrina Waters, Ph.D., Scientist, Pacific Northwest National Laboratory
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EPA's BOSC was reconstituted in 2014 with an Executive Committee and five subcommittees aligned with each of the National Research Programs. Part of the HHRA program is reviewed in conjunction with the CSS program. Each of the subcommittees met during 2016 culminating in an Executive Committee meeting in January 2017. The 2016 review focused exclusively on the CSS program.

The Subcommittee finds that CSS has made impressive progress in implementing the Strategic Research Action Plan (StRAP) over the past year. In addition, there has been admirable progress on specific areas highlighted in the Subcommittee's prior report recommendations. For example, the Subcommittee noted an extensive interdisciplinary effort to address the previously-noted gap in evaluating thyroid toxicity; significant efforts to evaluate chemical metabolites; an increased focus on ecotoxicology; and a laudable focus on exposure science. The impressive interim progress confirms the earlier assessment by the BOSC that the CSS Program "has the potential to be truly transformative of the work of EPA and of entire fields of environmental health science."

Overall, the Subcommittee concludes that CSS is doing the right science and is doing the science right. The Subcommittee further concludes that CSS is generally integrating its work well internally and with external partners and stakeholders. In-depth evaluation of the CSS research program did identify some areas that could benefit from additional resources, focus and improvement.

STRAP RESEARCH TOPIC AREAS

Chemicals are integral to the American economy and provide key building blocks for the many products that benefit society. Sustainable innovation and use of chemicals calls for making decisions and taking actions that improve the health of individuals and communities today without compromising the health and welfare of future generations. Smart new strategies for designing, producing, and using safer chemicals to minimize risks and prevent pollution is a priority for the U.S. Environmental Protection Agency (EPA).

The challenges to meeting this mandate are formidable: Tens of thousands of chemicals are currently in use and hundreds more are introduced into the market every year. Many of these chemicals have not been thoroughly evaluated for potential risks to human health, wildlife and the environment, particularly when considering the consequences of use over a chemical's life cycle (from production to disposal). Current toxicity testing methods for evaluating risks from exposures to individual chemicals are expensive and time consuming. Approaches for characterizing impacts across the chemical/product life cycle are data and resource-intensive.

Characterizing real-world exposures and early indicators of adversity in a way that allows proactive decisions to minimize impacts of existing chemicals as well as to anticipate impacts of emerging materials requires holistic systems understanding. Potential health effects from chemicals are associated with disruption to complex biological processes. For example, evidence is mounting that some chemicals disrupt the endocrine system. Some of these effects relate to chronic exposures to low levels of multiple chemicals. Prenatal and early-life exposures are of particular concern and may lead to health impacts across the lifespan. As a result, there is a need to shift the thinking about how potential for adverse impacts and ultimately risks are evaluated.

Today, EPA and its stakeholders are making decisions on chemical selection, design, and use at the national, regional, and local levels. States, communities, and consumers are demanding robust information on chemicals in products and are driving large retailers and industry to make changes. Tools for evaluating chemical substitutions and product alternatives are evolving to meet the demand for action. However, scientifically vetted approaches remain limited. New approaches are required to increase the pace at which relevant information can be obtained and integrated into decision-making, and to ensure that decisions are scientifically supported and sustainable. Key metrics that can be collected as early indicators of changes to the chemical exposure landscape are needed to preempt or rapidly mitigate unanticipated impacts.

To address these challenges, EPA's Chemical Safety for Sustainability (CSS) research program is leading development of innovative science to support safe, sustainable selection, design, and use of chemicals and materials required to promote ecological well-being, including human and environmental health, as well as to protect vulnerable species, lifestages, and populations. The ultimate goal is to enable the EPA to address impacts of existing chemicals, anticipate impacts of new chemicals and materials, and evaluate complex interactions of chemical and biological systems to support EPA decisions.

Working in conjunction with our partners in the EPA regulatory programs and regional offices, we have identified priority needs for information and methods to make better informed, timelier decisions about chemicals. CSS science is strategically scoped within four integrated research topics to support EPA priorities:

1. **Chemical Evaluation:** Advance cutting-edge high-throughput methods in computational toxicology and provide data for risk-based evaluation of existing chemicals and emerging materials.
2. **Life Cycle Analytics:** Address critical gaps and weaknesses in accessible tools and metrics for quantifying risks to human and ecological health across the life cycle of manufactured chemicals, materials, and products. Advance methods to efficiently evaluate alternatives and support more sustainable chemical design and use.
3. **Complex Systems Science:** Adopt a systems-based approach to examine complex chemical-biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals.
4. **Solutions-Based Translation and Knowledge Delivery:** Promote Web-based tools, data, and applications to support chemical safety evaluations and related decisions, respond to short-term high priority science needs for CSS partners, and allow for active and strategic engagement of the stakeholder community.

The *Strategic Research Action Plan for EPA's Chemical Safety for Sustainability Research Program* maps out a research program for the near-term with an eye toward meeting longer term needs to transform chemical evaluation. CSS scientific results and innovative tools will accelerate the pace of data-driven chemical evaluations, enable EPA decisions that are environmentally sound and public health protective, and support sustainable innovation of chemicals and emerging materials

CHARGE QUESTIONS AND CONTEXT

Charge Questions

Charge Question 1. Science

Are we doing the right research? Taking resource limitations into considerations, are there any significant scientific gaps?

Charge Question 2. Integration

Based on prior feedback from this Subcommittee, over the past year, CSS has focused on further integrating the program within and between projects. Please comment on the progress. Is the integration approach right? Are there other areas that should be enriched?

RESEARCH TOPIC AREAS

The bulk of the agenda was focused on evaluating the CSS portfolio relative to the Charge Questions. At the Subcommittee meeting, CSS presented on projects within its four overarching Research Topic Areas: (1) Chemical Evaluation; (2) Complex Systems Science; (3) Life Cycle Analytics Understanding; (4) Translation and Knowledge Delivery (See Figure below from CSS StRAP). In addition, the Human Health Risk Assessment program presented a brief review. The research topics serve as the overarching framework for more focused research projects that guide specific research and development activities. The research topics include:

Chemical Evaluation

Advance cutting-edge methods and provide data for risk-based evaluation of existing and emerging chemicals and materials.

Life Cycle Analytics

Address critical gaps and weaknesses in accessible tools and metrics for quantifying risks to human and ecological health across the life cycle of manufactured chemicals, materials, and products. Advance methods to efficiently evaluate alternatives and support more sustainable chemical design and use.

Complex Systems Science

Adopt a systems-based approach to examine complex physicochemical-biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals.

Solutions-based Translation and Knowledge Delivery

A fourth research topic focuses on translation and active delivery of CSS research and products, demonstration and application of CSS scientific tools, and knowledge delivery to EPA Partners: (1) Promote Web-based tools, data, and applications focused on tailored solutions to support chemical safety evaluations and related decisions; (2) Respond to short-term high priority science needs for CSS partners; and (3) Allow for active and strategic engagement of the stakeholder community.

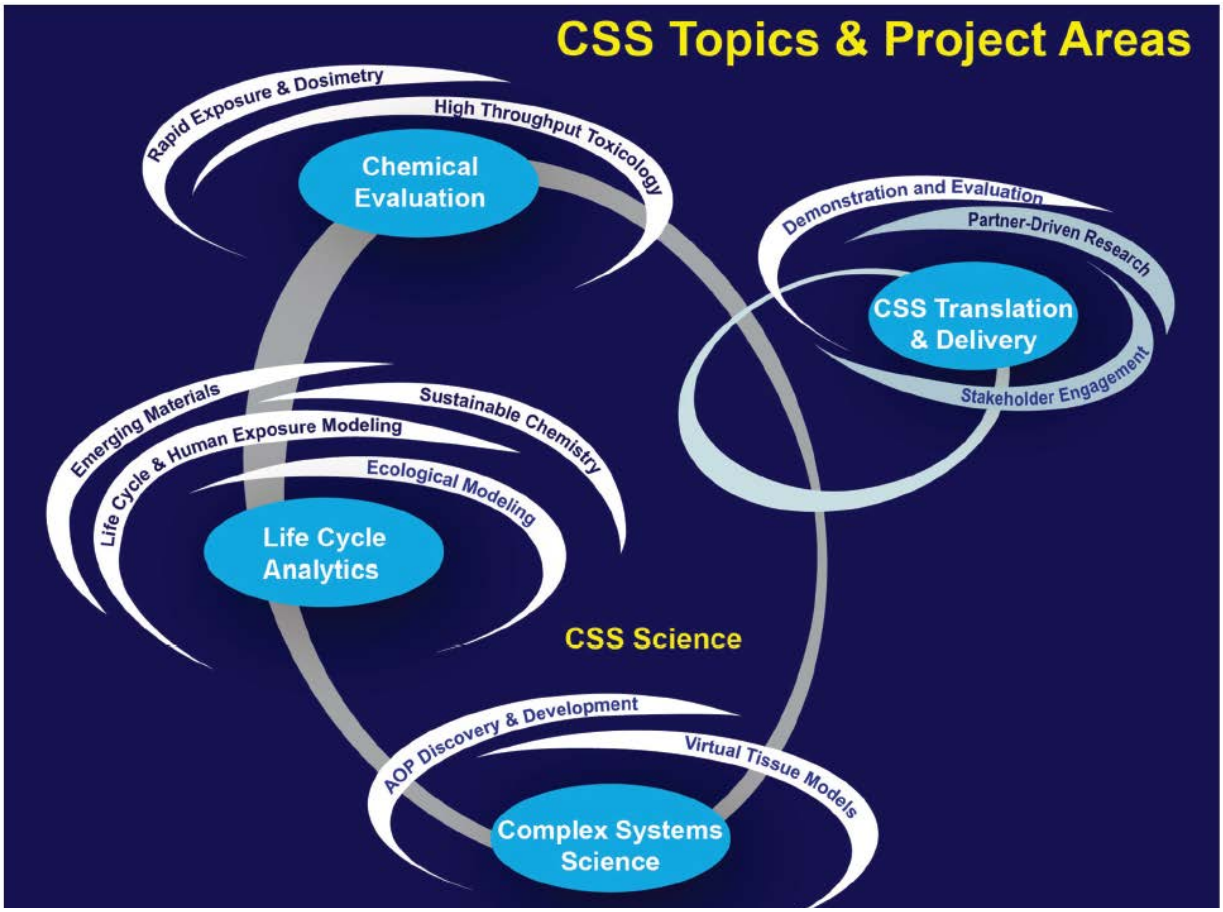

Figure 1. CSS Research Topics and Projects

SUBCOMMITTEE RESPONSES TO CHARGE QUESTIONS

Charge Question 1: Science

Are we doing the right research? Taking resource limitations into considerations, are there any significant scientific gaps?

Chemical Evaluation

Donna Vorhees, Katrina Waters, Chris Gennings, Som Somasundaran

CSS continues to make remarkable advances in their chemical evaluation strategies including in High Throughput Toxicology (HTT) and Rapid Exposure and Dosimetry (RED). Both programs are to be commended for "doing the right science" with integration across programs.

High-Throughput Toxicology

The key tasks outlined for the HTT research program addressed reviewer comments and gaps specified in the BOSC 2015 report: assay performance, new assay development and approaches to incorporate metabolism. Assay performance guidelines are being developed using a fit-for-purpose evaluation of

assays with sets of reference chemicals. Developing reference sets is essential to provide confidence in the HTT data for chemical prioritization and to eliminate unreliable assays from the testing battery. It is also essential to ensure that the quality metrics for assay performance be incorporated into the assay annotation that is disseminated with the data on the CSS dashboard. The Toxicity Forecaster (ToxCast) Assay Annotation Database will be important for use of HTT data by program and regional partners, as well as other stakeholders, for risk-based decisions.

In addition to assay performance, there is the concern that several assays measure the same target and, unless they represent distinct modes of action, may not provide sufficient additional information to justify the cost. It would be valuable for CSS to develop a balanced strategy to both retire existing assays that may not add sufficient value to the program while bringing on board new assays that add important biological content to the hazard identification mission.

Progress in new assay development was demonstrated for high priority outcomes related to thyroid hormone activity and neurodevelopment. Because thyroid active chemicals rarely interact directly with the thyroid hormone receptor itself, several alternate targets of thyroid disrupting chemicals were identified for assay development and validation. The HTT program is currently screening the 1900+ Phase I and II ToxCast chemicals through new Molecular Initiating Event (MIE) assays for inhibition of the sodium-iodide symporter, thyroperoxidase and iodothyronine deiodinase type I, and three more assays are currently in progress. Concurrently, for the neurodevelopment outcomes, assay development is focused on increasing levels of biological complexity to capture cell-based morphological features, functional networks in organotypic cultures using micro-electrode arrays, and whole organism behavior in zebrafish. These data are increasingly complex compared to single measurement, single time point assays and will require new data analytics approaches to go beyond single EC50 values or arbitrary “epochs” of time to capture dynamics, intercorrelated endpoints, and ultimately provide quantitative relationships between the assay measurements for an Adverse Outcome Pathway (AOP) network evaluation.

Another comment from last years’ report was the recommendation to use complex systems research to define new assays for HTT that are useful for risk assessments. There were several examples of transcriptomics technologies being used in a discovery mode for the identification of new modes of action (MOAs) to add assays to the HTT screening program, to identify biosignatures for cancer AOPs, and as a basis for defining nanoparticle bioactivity. However, these efforts appear to be using gene expression itself as the assay with no relationship to a functional, key event process based upon the AOP framework, or even based upon a known MOA associated with an apical endpoint. Such an approach may be useful for prioritization. In order to be useful for risk assessments, however, HTT assays must be supported by qualitative or quantitative information that links the data to apical endpoints. One example for how this could be done was presented as an integrative, data mining approach that would combine transcriptomics data with HTT and in vivo data to inform de novo AOP development. It would be good to see a unifying strategy for how transcriptomics data are being used in CSS for new assay development using the AOP framework.

A third area of priority is the incorporation of biotransformation into the HTT screening process. The program is using a two-prong strategy: one is extracellular and uses beads that incorporate S9 fraction for metabolism in media or buffer prior to other assays, and the second is intracellular and incorporates the generation of cells that are metabolically competent. Incorporation of an S9 fraction is a standard bulk approach to identify if biotransformation is a key event that alters toxicity either way (increased or decreased). The intracellular protocol is using cell populations that incorporate panels of Cytochrome P450 mRNAs into HEPG2 cells as a research concept that attempts to capture the complex of enzymatic transformation in a more targeted way. However, the potential number of enzymes, cell types and species

required to comprehensively capture biotransformation of chemicals with this approach could quickly become financially infeasible. One possibility might be to partner with the existing computational approaches for predicting biotransformation to prioritize the panel of enzymes, other critical cell types, and important species-specific effects.

Rapid Exposure and Dosimetry

The advances in exposure modeling since last year are striking. The efficient and creative use of existing data should prove beneficial to multiple EPA programs as well as non-EPA organizations. An example is the integration of ExpoCast exposure predictions with ToxCast-derived receptor bioactivity converted to dose. This integrative approach provides exposure estimates for many chemicals that fall well below those associated with bioactivity, thus reducing the number of high priority chemicals for more detailed analysis. This information has obvious importance to various EPA programs allowing them to prioritize chemicals of most concern. In addition, some form of this information would be useful for the public in understanding the significance of any exposure they might be experiencing. The computer product scan (and reliance on other similar but less comprehensive efforts), the non-targeted analytical chemistry, and forensics have the potential to feed into multiple EPA programs. The forensics work illustrates a particularly interesting approach to combining available data, machine learning, and good analytical chemistry to identify and ideally provide an understanding of the sources of exposure thereby directing opportunities to reduce problematic exposures that previously were difficult to identify. The Life Cycle-Human Exposure Modeling (LC-HEM) effort (discussed further below) simulates exposures not to just industrial and commercial releases but also to personal care products and household products used indoors, leading to an understanding of the dominance of near-field exposures for many chemicals. The exposures can be averaged over minutes to years, allowing for acute and chronic health evaluations.

The impressive exposure simulation work builds on previous EPA efforts (e.g., Stochastic Human Exposure and Dose Simulation [SHEDS]) and incorporates exposure data compilations in an efficient and transparent way. But no matter how impressive they are, as with any modeling effort they need to be evaluated/validated with real-world monitoring data and should be continually updated and evaluated as product compositions change using information from manufacturers, product testing and exposure measurements.

Chemical Mixtures

Human and ecological exposures within all natural systems are multi-particle and multi-chemical, thus, risk assessments ultimately need to be based in real world mixtures rather than single chemicals. This is particularly important since toxic materials can become nontoxic and vice versa by transformation to other chemicals or physical states due to reactions of chemicals within mixtures or from lifecycle processes (aging, degradation, transformation) and their toxicity can be altered due to synergistic or antagonistic interactions. Further, interactions can be dynamic in nature, for example the chemical form and reactivity in aqueous media vary with respect to temperature, pH, ionic strength, water hardness and dissolved oxygen content. Nanoparticles also can behave differently in the presence of mixtures and other chemicals particularly when they aggregate due to associations.

Dr. Wambaugh noted how exposure simulations could benefit cumulative exposure or risk assessments. He commented that his group will look for common chemical mixture exposures that emerge from exposure simulations. Evaluation of the mixtures themselves using HTT approaches may better predict toxicological effects than do assays of individual agents. An interesting and testable research question relevant to the HTT program is to compare the potency of multiple single chemicals in HTT assays with

the potency of mixtures when the toxicological information from such chemicals are combined in a way that reflects actual human exposure.

The next question is: How relevant or useful are these assay results to human risk assessments? Wetmore et al. (2013) compared points of departure based on *in vivo* data with points of departure based on high throughput assay data for individual chemicals for hazard identification. The in vitro points of departure were systematically lower than the in vivo points of departure. Similar analyses could be performed for chemical mixtures with *in vivo* toxicity data. One approach to better assess real world conditions is to expand the analysis to incorporate biomonitoring data documenting exposure to similar chemical mixtures.

Generally, the CSS could make advances in focusing on human-relevant mixtures by building links with ongoing National Institutes of Health (NIH)-funded cohort studies. For example, the CHEAR (Child Health Exposure Assessment Resource) and ECHO (Environmental Influences on Child Health Outcomes) NIH initiatives will have untargeted exposure assays across multiple matrices on pregnant women and children – important exposure estimates to vulnerable populations. The plan to link the studied chemicals in ToxCast to the library of peak locations in biomonitoring samples illustrates the transparency of the CSS program.

A great example of incorporating real environmental mixtures into the HTT screening process was demonstrated through the Great Lakes Surveillance project. This team is using water samples from U.S. streams directly in pathway-based bioactivity screening using the Attagene subset of ToxCast assays. The samples also have quantitative measurements for ~800 contaminants that are being used to correlate contaminant levels with bioactivity measurements and to prioritize chemicals of concern for further testing. The team has also developed an Exposure Activity Ratio to prioritize sites for more intense and focused investigation. While only about 100 chemicals measured in these samples overlap with the ToxCast database, this provides a unique opportunity to evaluate the cumulative effects of these mixtures on bioactivity and to prioritize new chemicals for screening through the HTT program.

Evaluation Against StRAP Objectives

Overall, the HTT has made significant progress on the StRAP objectives. In the area of building knowledge infrastructure, data are or will be publicly accessible. Different types of data have been combined in creative ways to identify realistic human exposures. In developing tools for chemical evaluation there has also been very good progress. Multiple EPA partners reported how high throughput data had already been helpful to their programs. In the area of research translation and active delivery there is more to do on developing solution-based approaches (e.g., challenge of translating from in vitro assay to whole organism response) but the program is taking critical first steps in accordance with the StRAP.

Recommendations

Recommendation 1.1: Articulate a unifying strategy for how transcriptomics and other data are being used in CSS to inform new assay development using the AOP framework.

Recommendation 1.2: As appropriate, retire existing assays that may not add sufficient value to the program while bringing on board new assays that add important biological content to the hazard identification mission.

Recommendation 1.3: Evaluate whether assays of single chemicals over- or under-predict the effects of combined exposures to mixtures.

Complex Systems Science

Jim Stevens, Rebecca Klaper, Dale Johnson, Jennifer McPartland

The Complex Systems Science Program (CSSP) has made significant progress on their strategy since the last review and it is obvious that it is doing the right science. Most notably the Virtual Tissue programs have made important advances during the past year particularly in the developmental biology field with significant enhancement through external partners from the Science to Achieve Results (STAR) granting mechanism, which demonstrates the strength of using STAR as a tool. The Virtual Tissue program is currently focused on understanding the potential hazards and risks of environmental chemical exposures to vulnerable populations, such as young children and pregnant women, who are exposed to chemicals during critical developmental stages. The Virtual Tissue Matrix (VTM) projects were highly responsive to feedback from last year to provide an experimental proof of concept to demonstrate experimentally the linkage between model predictions and apical outcomes.

Other efforts such as the Adverse Outcome Pathway Discovery and Development (AOP-DD) program have continued to develop a framework that is beginning to gain traction within the scientific community, and the fact that it originated within EPA should be commended. While CSS has worked to expand the number of putative AOPs available and the web portal has undergone substantial revisions to increase the accessibility of the AOPs, the number of Organization for Economic Cooperation and Development (OECD) approved AOPs is limited thereby reducing the capability of applying AOPs to evaluating hazards. The Complex Systems Science initiative as a whole continues to have cross-cutting impact for a number of important areas of the CSS mission including effective implementation of complex modeling methodologies across programs.

CSS has done an outstanding job of demonstrating integration of the CSSP both within and between CSS projects as well as across EPA regions and offices with demonstrable impact. Overall the science was impressive, the progress in a year was excellent, and the focus on the hazard identification mission was clear. The BOSC CSS Subcommittee strongly endorses the CSSP strategy and applauds the progress. Specific comments are addressed in three sections below:

Integration and Extrapolation Across Species

As the read across from known chemicals to new chemical structures and structural classes is integral to the HTT mission, reading across species is an equally critical area and fundamental to complex systems science. The two primary components of CSSP are VTM and AOP-DD (Figure 1; FY16 CSS StRAP). Although the strategy does not highlight a specific CSSP focus on developing a systems biology level approach to extrapolating hazard identification and eventually risk across species (hereafter termed 'read across species'), it is important to note that the concept and execution to date of the AOP framework concept as well as the Ecotoxicology (ECOTOX) database and Sequence Alignment to Predict Across-Species Susceptibility (SeqAPASS) tools originated with the ecological risk group which by its nature evaluates the impacts of chemicals across many types of species. As a result, some of the most mature AOPs for example, highlight important environmental exposure scenarios for many organisms. These include: endocrine disruptors in aquatic environments and their impacts on fish and other organisms, and pesticide exposures. This highlights the opportunity and the need to link the various efforts in this program to make 'read across species' process a reality. There has been significant progress in developing links among the different tools in the CSSP program within the CompTox database framework. However, linking effects across species appeared to be limited to the SeqAPASS tool. Strengthening connections through biological pathway linkages across species through some of the other tools (ECOTOX, AOP) would be extremely valuable not only for the science but for various programs. In addition, a missing element in the

presentations was clarity on how appropriate linkage will be established for extrapolation to human risk from ecological risk. Using these efforts to develop a link between the two would enhance the science needed for decision making.

The BOSC CSS Subcommittee noted the CSS strategy should include systems modeling across species for both ecological and human hazard identification. For example, for highly conserved biological response pathways it is important to understand similarities and differences in biological response networks from *in vitro* data and models to *in vivo* read across phyla and classes. This will also be important when mixtures of chemical compounds are added to screening efforts and predictions and validation of additivity, synergism, or reduction of effect are needed. Acknowledging that significant resources may be necessary to gather new datasets from model organisms, CSS should consider highlighting these opportunities and augmenting internal constrained resources through mechanisms such as additional STAR requests for applications (RFAs). CSS leadership acknowledged the BOSC CSS Subcommittee's general comments regarding the importance of reading across species and indicated this is an important component of the CSS strategy; the BOSC CSS Subcommittee encourages CSS to address this topic at future meetings.

Specific comments highlighted during discussion generally related to advancing the ecological risk toolkit in ways that link read across technology to other CSSP focus areas and creating links across different tool within the large CSSP project:

- SeqAPASS: This tool is an interesting attempt at cross-species evaluation and the tool itself has progressed in its development since the last review. The committee has some concerns as to the emphasis of CSSP on this tool as a major determinant in predicting chemical safety. There were questions as to how a one dimensional estimation of interaction of a chemical and a sometimes putative protein prediction would properly evaluate the impacts of a chemical across species. In addition the predictive capabilities seemed limited as many chemicals have impacts beyond direct interaction with a receptor on a single protein. The committee thought other efforts that focus on more holistic global expression pathways or interactome quantification more appropriately characterize potential impacts and worry this tool is too simplistic. If there was a way to couple this tool to some other efforts to demonstrate experimentally its accuracy in prediction, the utility may be better evaluated.
- ECOTOX database: The ECOTOX database is an excellent tool and highlights a unique aspect of what EPA does that no other agency does in order to address its mission. The plethora of curated data in this tool allows for rapid retrieval of information from an extensive corpus gathered in the scientific community for a given chemical. It is readily accessible and easy to use. There are a couple of activities (some currently at least discussed or being considered) that would really strengthen this tool and make it more effective and able to be used across more activities necessary for EPA to protect ecosystems within the US. More resources should be dedicated towards:
    - Including more information on endpoints other than LC50, acute toxicity assays. This should include more data on effects of chronic exposure that are much more relevant to real world scenarios than evaluating LC50 or acute exposure assays. In addition, other endpoints such as: immunological, reproduction, tumor development, developmental endpoints, and behavior are much better indicators of real impacts seen in the environment, and provide much more power than acute necrosis which often is the default endpoint for modeling the impact of chemicals and for grouping chemicals based on similarities of health endpoints. There is a current effort by one contractor to go through and add other selected endpoint data. This is not sufficient to understand chronic effects.

- Connecting ECOTOX to the CompTox dashboard. This was mentioned as an effort going into the future but it should be a priority so that after (1) is underway more data is linked within the CompTox framework and can be used for modeling efforts and links to high throughput screening (HTS) data. The ECOTOX database should also be linked to PubChem either through the CompTox dashboard or before to provide better links to chemical data and links of publications in each database.
- AOP Wiki: The AOP concept and Wiki generated a full discussion within the committee. To represent the discussion and recommendations fully we have more discussion of this tool below (please see the section below).

In summary, the importance of reading across species is understood by the CSS leadership and recognized as an important topic. Resources may be constrained and it seems unlikely that new resources will be available to pursue this important topic more aggressively. CSS is encouraged to integrate existing resources to the extent possible to address this challenge and to include this overarching goal in its future objectives for the StRAP.

Virtual Tissues (VTM)

The VTM focus on developmental processes dovetails nicely with the endocrine disruptor screening program and ToxCast. Incorporating external research capabilities at partner institutions facilitated by the STAR grant mechanism has significantly enhanced this program by adding the broader capacity and expertise of academic institutions. Indeed, this is an excellent example where the STAR grant program has accelerated progress by effectively accessing external innovation. Modeling within this program is quite sophisticated; the addition of experimental approaches to validate models was completely responsive to BOSC CSS Subcommittee comments from the previous review. A gap noted by the BOSC Subcommittee was the limited use of tissue models, efforts that would exceed current capacity in the program. The committee does encourage more STAR mechanisms and other collaboration efforts to cover key gaps wherever possible.

During discussion there were many detailed comments on this program most of which focus on the positive development of this program to date, with some suggestions highlighting the value of external partnerships:

- CSS is encouraged to consider an 'after action' review detailing the importance of STAR funding in VTM progress. For example, what might have been the real costs and time necessary to 'build it here' versus the STAR external funding mechanism? This type of mechanism could offer additional opportunities for CSS to access innovation in areas where internal programs are at capacity such as quantitative systems pharmacology modeling and systems biology.
- The Virtual Embryo project demonstrated a cell-agent based model that included a putative AOP for medial edge epithelial seam breakdown to produce a cleft palate phenotype. Likewise, the team is modeling a neurovascular unit using an AOP for the microcephaly phenotype with an agent-based simulation of cellular interactions. While the AOPs themselves have not been verified with regards to the proposed quantitative relationships for the key events, it would provide a strong proof of concept to simulate the effects of chemicals that are known to produce these outcomes using existing dose-response data. If VTM can verify that even at this early stage of model development, key event assay data and animal study data from the Chemical Evaluation Program can be used to model specific chemical impacts using the model it would go a long way to build confidence regarding the value of using complex system models in risk assessment.

- The organotypic human embryonic morphogenesis fusion model using stem cell derived cellular cultures has developed to a point where screening can start on selected chemicals, again using a validation source of information. The platform as developed can also be used to screen mixtures of compounds which will be important to model actual environmental exposures. The platform does have the potential to screen and predict birth defects in a number of tissues and organs derived from induced pluripotent stem cells. The models for mesenchymal transitions in morphogenesis have developed to a point where key biomarkers will be established and screening can begin. This will eventually lead to highly significant computational models for early human cardiac development. The cell-based assays for nervous system development utilizing rat, mouse, zebrafish, and human samples measuring endpoints of key neural development events along with brain-on-a-chip models offer an example of excellent cross species endpoint evaluation. Using high content imaging and collecting data in a dynamic fashion creates a model that shows the possibility of collecting data to model neural network formation and function using continuous data collection. The extremely interesting work on the analysis over time of cell morphology in culture systems has broad and wide-ranging potential to reduce the variability and uncertainty in modeling developed from cell culture screening.
- In the post-development organ toxicity field, it is well known that the development and commercialization of *in vitro* models for use in toxicity screening have blossomed in the past few years, particularly in the area of predicting drug candidate liabilities during early drug discovery and development. This includes the expanding organ-on-chip technologies, with several organ-on-chip products and recent collaborative agreements with contract research organizations. This potential work for CSS predictive toxicity more centered on post developmental "adults" can be accomplished using outside collaborators with validated models to develop large scale databases of endpoint information for computational models.

Adverse Outcome Pathways (AOPs)

The AOP initiative is fundamental to the CSS mission and cuts across multiple programs as well as extending to support the HHRA mission. The approach being taken by CSS within the AOP program has the potential to have a major impact if it is able to generate AOPs for a much greater number of pathways. CSS is focused on the right topics and science in taking on this enormous challenge, which includes bridging the AOP concept and existing mode-of-action frameworks with complex systems biology modeling while at the same time achieving international harmonization of best practices. The AOP Wiki web portal enables delivery of knowledge to the scientific community and vice versa and fulfills a national and international interest. Collaborations with OECD to build a community of researchers that are adding to the Wiki is a reasonable hedge against random addition of information that may be unreliable, but the BOSC Subcommittee encourages EPA to advance putative AOPs awaiting OECD endorsement within the Wiki since it aids in pointing to new research directions. Overall, the AOP framework will shape risk assessment and help move to a systems level understanding across species. A number of topics were discussed by the BOSC CSS Subcommittee:

- IT resource and manual curation limitations: A true wiki that allows crowd sourcing would far exceed CSS capacity to moderate, thus the AOP wiki has moved toward a content delivery platform. This is appropriate for the resources available but does limit the power of a true wiki format for AOP formulation. Despite the appeal of crowd-sourcing approaches the BOSC CSS Subcommittee feels the current approach is the right approach to move the project forward and establish a corpus of AOPs available for consideration and comment.

- AOP characterization and validation processes: CSS is encouraged to review both process and terminology (e.g., qualified, valid, putative, endorsed, etc.) to aid movement of AOPs from inception to international endorsement (used here to mean through OECD) while balancing the need for accelerating application and reflecting current biological understanding. OECD endorsement is desirable but takes time. The challenge is to advance application of the science while the OECD endorsement process proceeds. AOPs should not be static, thus, CSS should consider how to be flexible and evolve AOPs and the AOP process by integrating new understanding of etiology and pathogenesis relevant to health issues. This can be accomplished in a manner that is transparent and scientifically sound while adhering to the OECD process. Allowance for knowledge relevant to risk assessment captured by AOPs that are not yet officially endorsed can enable the latest science to be reflected in the AOP framework, filling knowledge gaps and recognizing new biological discoveries while increasing external engagement (e.g., by academic researchers) in the construction of AOPs. CSS should consider implementing a process with identified terminology that strikes an appropriate balance between nimbleness and international harmonization of AOPs to advance application.
- AOP Strategy and AOP WIKI Content: The AOP Wiki project has made good progress toward the design of V2.O of the wiki. As noted above, the strategy has shifted from wiki technology toward a knowledge delivery framework to simplify implementation. The web platform has undergone a substantial redesign to improve functionality. The committee did acknowledge the scores of new AOPs under development since the 2015 BOSC CSS Subcommittee review but questioned if there was a lack of engagement by the basic research community in building these AOPs, which could represent a significant limitation. CSS should consider strategies to improve engagement across the scientific community including reaching across into human toxicology and disease etiology frameworks to enhance this tool. For example, CSS could reach out to a group of investigators, which included EPA ORD scientists, that sought to identify "key characteristics" of carcinogens (e.g., induce oxidative stress, alter DNA repair or alter genomic stability, modulate-receptor mediated effects) toward creating a framework for integrating mechanistic data into a carcinogenicity classification system.[1] Given the scope and nature of their effort, there may be an opportunity to construct putative AOPs around cancer, and additionally explore how data emerging from CSS cancer toxicogenomic studies relate (or not) to the identified characteristics. The AOP strategy is integral to the CSS strategy and extends into HHRA, thus data-driven AOPs based on solid science are critical. Over the next year CSS is encouraged to move as many AOPs as possible through various stages of technical development and scientific consensus, and submit products appropriate for OECD review in the future.
- Quantitative Modeling: CSS noted that AOPs are not quantitative models. Nonetheless, there is a clear need to extend toward exposure response models (e.g., physiologically based pharmacokinetics [PBPK] and toxicokinetic-toxicodynamic [TKTD]) that link exposure to TD markers of effect and systems level responses. There is value in the biological knowledge framework particularly when there are gaps or significant uncertainties, but illustrating how the existing AOP knowledge framework will be moved toward quantitative exposure-response modeling will be critical for moving from hazard identification to risk assessment.
- Systems approaches and AOPs: CSS should continue working to create synergy between other areas of the complex systems science programs and the overarching AOP initiative. The current strategy to

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[1] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert P, Hecht SS, Bucher JR, Stewart BW, Baan R, Cogliano VJ, Straif K. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124:713–721; http://dx.doi.org/10.1289/ehp.1509912

aggregate known information into a knowledge management AOP framework is effective. However, an additional systems-level approach can also be pursued to identify new pathways and response networks, as noted above in the species extrapolation section, to enhance the AOP framework.

Summary

CSS is making excellent progress and bringing relevant cutting edge science to bear on the Research Objectives. Although there are gaps, the BOSC CSS Subcommittee strongly endorses the strategy and commends both leadership and the staff for making remarkable progress since the 2015 review.

The CSSP is meeting both near-term and long-term aims in supporting the overarching CSS research objectives. The AOP Wiki project is an exciting project and building this knowledge infrastructure is critical to the CSS mission and to its ability to impact other EPA programs. Relative to other types of dashboards and tools built around more structured data, knowledge delivery represents a new challenge.

In the StRAP area of developing tools for chemical evaluation the CSSP really shines. The VTM program is extending capacity through the STAR program and engaging leading scientists nationally and internationally to advance tissue modeling technology. They are well integrated into the overall mission of CSS and their reach is poised to extend into the HHRA. CSSP is recognized as a leading (if not the leading) organization advancing complex systems understanding into environmental risk assessment. Their science is outstanding, their reach is broad and they are having impact.

Translation and active delivery is a key strength of the CSSP. It was clear from the program and regional office engagement session that CSSP output is having real impact outside CSS and is supporting the risk assessment mission of the agency. It was gratifying to hear from scientists focused on the most basic research problems that they considered it part of their mission and responsibility to show impact

Recommendations

Recommendation 1.4: Consider creating a pipeline of scientifically sound and accepted AOPs awaiting OECD endorsement.

Recommendation 1.5: Continue to advance the science, including the STAR program, and look for points of entry to application while extending the approach to other organs as resources allow.

Recommendation 1.6: Extend complex systems approaches into model organisms and intact systems to bridge the outstanding work done in vitro into read across species applications commensurate with AOP areas of focus for both ecological and human hazard identification.

Recommendation 1.7: Continue focusing on engagement wherever possible to illustrate the power of applying systems science to risk assessment.

Lifecycle Analytics

Gina Solomon, Mark Wiesner, Rebecca Klaper, Som Somasundaran

The Subcommittee reviewed the Life Cycle Analytics (LCA) Project on November 17, 2016. The review included presentations on LC-HEM, Emerging Materials, Ecological Modeling (EcoMod), and Sustainable Chemistry (SustChem). The Subcommittee also reviewed poster presentations from each of these projects and participated in demonstrations of CPDat, and the Chemistry Dashboard.

At the conclusion of the day-long in-depth review, the Subcommittee concluded that the Life Cycle Analytics project is doing the right research and did not identify significant scientific gaps. The Subcommittee also concluded that although there is generally very good integration between this project

area and other projects within CSS, there is sometimes a lack of clarity about the links between various activities within the LCA project. Overall the LCA project created the impression of a lot of interesting and important research efforts that are loosely linked together under the heading of LCA, but without a clear narrative within the project area. Some specific comments include the following:

Database Tools

The Subcommittee was shown an ensemble of databases and accompanying "dashboard" tools that are either linked, or are on the path to being linked, in an overall cheminformatics effort. These tools and databases are linked with the objective of screening new and existing chemicals, prioritizing testing, performing alternatives assessments and life cycle analysis. Examples of tools under development that illustrate the breadth of this effort are: (1) the CompTox dashboard which provides chemical information look-up and embedded models for calculating chemical properties as well as links to EPA and publicly available data bases; (2) a chemical transformation simulator for predicting transformation pathways for organic chemicals; (3) an alternatives assessment dashboard for evaluating chemical alternatives, including chemical synthesis and release to the environment; (4) Human Exposure Model Software that provides information on the chemical composition of consumer products, allows for the generation of various impacted populations and that can be interfaced with an agent-based model for product use, models for far-field transport and fate and dose estimation; (5) a nanomaterials knowledge base being designed for decision support on nanomaterial production, releases, transport and transformations, exposures and effects; and (6) tools for ecological modeling that estimate spatiotemporal distributions of chemicals and ecological receptors, predict organism-level doses and populations-level effects. The quality of the products in the dashboard to-date is outstanding and work to accomplish the ambitious goals for linking many of these elements is well underway.

The CompTox dashboard creates a broad umbrella for accessing diverse databases ranging from the ToxCast and PhysChem databases to chemical use, creating an ideal platform to study and evaluate the chemical space for over 750,000 chemicals. The RapidTox dashboard can be accessed through CompTox (and vice-versa) and integrates data on chemical properties, hazard, and exposure. The chemical space is enhanced by ToxCast data, and ExpoCast data on exposure, CPCat/CPDat data on chemical use, as well as toxicokinetics information and ToxPrint chemotypes using the query language, CSRML. This is a unique platform to create read-across (extrapolation) functions and to identify potential alternatives to compounds exhibiting certain hazard traits. These products will easily become valuable tools in the search for safer chemicals and in the green chemistry process of safer chemical design.

The Subcommittee was shown a slide on "Software Integration" (slide 4 in Dr. Stevens' presentation). The slide was useful in showing the relationship among several CSS products, and its expansion to all CSS products would help users navigate among them. A user of any product needs to know: (1) how they are related conceptually; (2) the sources/quality of data incorporated by each; and 3) the overlap among data sources used by each. Ideally, the relationships could be shown simply in one graphic like Slide 4, accompanied by a brief explanation to help users to navigate easily and knowledgeably among the impressive set of products. The Subcommittee notes that a similar recommendation was made in our prior report.

Life Cycle Human Exposure Modeling

The LC-HEM products are built upon two decades of exposure modeling and life cycle assessment research, and they are now pushing the science forward in leaps and bounds. CSS is using state-of-the-art modeling and data integration practices that keep their efforts at the forefront of the field. The

Subcommittee was pleased to note that CSS is enhancing the current approach to exposure assessment within LCA by capitalizing on the vast exposure modeling expertise at ORD. They have proposed a novel way of using many existing databases to develop longitudinal descriptions of human behavior and exposure in relation to consumer products. They are proposing to use novel software designs to efficiently enable top-down data mining from linked open data sets.

The Subcommittee was impressed at the LC-HEM effort to model exposures over minutes to years, allowing for acute and chronic health evaluations. This effort builds on previous EPA work (e.g., SHEDS) and exposure data compilations in an efficient and transparent way. The LC-HEM can be used to predict the population with the greatest exposure from the products being considered, and to guide which chemicals may be of greatest concern based on product use and population characteristics. This approach will lead to a better understanding of chemical substitution in products and the ability to better guide alternatives analysis. This work clearly merits continued emphasis.

There is great evidence of this project area's integration with other components of CSS. The LC-HEM is using data generated by the RED and Demonstration and Evaluation (D&E) projects. LC-HEM is also jointly working with the emerging materials group on extending CPDat to include nanomaterials. Outputs from LC-HEM are being used in the CompTox Dashboard. This integrated approach can facilitate alternatives assessment by employing an iterative process to optimize the decisions for the characterization of risk to alternate chemicals in products. Within this project the life cycle analytic exposure model can be used to predict the population with the greatest exposure from the products being considered, to guide which human health effects are of greatest toxicological concern based on product use, life cycle of the product and the exposed population. This effort could further be combined with other exposure models that could predict background exposure levels to a chemical and estimate the increment of change from substituting an alternate chemical in the product. This approach will lead to a better understanding of the sustainability of chemical substitution in products and the overall population exposures associated with those chemicals.

The LC-HEM appears to currently focus less on the "end-of-life" of a product. This is a potential gap because the disposal phase of the lifecycle may disproportionately affect some communities, regions, or even states. The Subcommittee was encouraged to hear that some of these issues will be addressed in efforts focused on the recycled product stream and reuse of products. Some of the databases that are currently being used are fairly old, like the Consolidated Human Activity Database (CHAD). Are there efforts to update these databases or assess if they are still relevant? Finally, approaches that focus on mining existing EPA databases (e.g., the Toxic Release Inventory [TRI]) are by necessity limited to chemicals that are already on reporting lists and in these databases. It is critical to continue to complement these datamining efforts with predictive efforts in order to cover a broader chemical space. Efforts should continue to integrate the various hazard and exposure focused platforms describing chemical and materials behavior across the life cycle.

Emerging Materials

Relevant work on modified and engineered nanomaterials is well underway. Excellent progress has been made in the short period since the Subcommittee's prior meeting. The nanotechnology program is small but the focus on providing decision and discussion points within its tools is valuable.

There are multiple conceptual barriers to treating nanomaterials as simply new chemical elements rather than more complex secondary phases. For example, wettability is critical for determining interaction with biological lipid membranes of cells. Toxicity of nanoparticles has been reported to depend on the size,

shape, asperity, charge and heterogeneity of the particles as well as presence of other particles and chemicals. Toxicity of carbon nanotubes (CNT) has been shown to be dependent on length in relation to the size of cells. Indeed, when aggregated they are less toxic. To prevent aggregation, stabilizers are used. The current study involves sodium dodecyl sulfate (SDS) as a stabilizer. It is to be noted that CNT are stabilized not only by SDS but also by hydrophobically modified polymers.

The database for this program is admirable for compiling information. However toxicity information on nanomaterials should eventually be placed within the CompTox database effort even given the needed additions of descriptors for the nanomaterials and the form they take in various exposure conditions. Linking it also to the products database (CPDat) where any nanomaterial information is available would also be valuable for risk assessment and modeling.

Other challenges will be encountered in the currently planned CompTox effort to support "ambiguous" materials such as mixtures and polymers. The nascent effort to evaluate modified biological organisms strikes the Subcommittee as especially daunting, both because the science in this area is barely emerging, and because it is well outside the current areas of expertise represented in CSS. Absent additional budgetary support, it will be very challenging to make substantial progress in this area.

The efforts to characterize nanoparticle transformations following their release into the environment in order to understand their life cycle and the resulting exposures as they age should remain a consideration of this work.

Ecological Modeling

The ecological modeling tasks were particularly impressive given the small number of full-time equivalents (FTEs) involved in these projects. Their work was diverse and ranged from large-scale catchment modeling of pesticides to linking potential extrapolations of AOPs from one species to another to landscape exposure models. The group has been largely focused on pesticides due to priorities and mandates within EPA that include predicting impacts to endangered species. Pesticides are also a reasonable area of focus because known mechanisms of action exist for the chemicals considered, which could make modeling across the ecosystem a bit easier. Due to resources as well as needs, they have focused largely on "off the shelf" modeling programs to determine if these work well enough for these purposes. The team seems to be asking very good questions of these models and making an effort to translate the laboratory mechanistic science of AOPs, and HTS into larger scale predictions. This effort is still in development so it will be interesting to see updates in the future.

There are a number of focus areas for FY2017 and activities seem to be focused on evaluating potential metrics. This approach seems logical but the Subcommittee suggests that it would be helpful to demonstrate a plan as to how each piece fits together to feed a bigger prediction of exposure and effect. What is visible now in the posters and presentations is an extensive list of projects and while one can see how each individual piece could be important, developing a schematic about what we are currently missing and how each model builds into a larger assessment framework and prediction would be very beneficial. In addition it would be good to see how the predictions may be tested to determine where the models fail or need more information so that these measurements could be built into future lab and field work. Doing this would provide a vision of how this part of the program provides a larger contribution to chemical safety and sustainability, particularly a full vision as to how these efforts take laboratory science into the field.

Sustainable Chemistry

The cheminformatics project's case studies on ToxCast and skin sensitization were especially notable as impressive endeavors. The sheer amount of work involved in cleaning up the Chemical Abstract Service (CAS) numbers of chemicals, and the creativity displayed in evaluating the inter-linkage between the chemistry and the ToxCast data show that this work is certainly worth pursuing.

The Chemical Transformation Simulator effort is clearly important and is one of the responses to concerns previously voiced by this Subcommittee and by others that ToxCast focuses almost exclusively on parent chemicals and that metabolites and breakdown products also need to be evaluated. The Subcommittee was impressed with the effort to curate the transformation pathways, but also raised some concern that the magnitude of the effort of manual curation may be too large to be realistic given the limited resources in the LCA project. Developing more rapid approaches, such as machine-learning, instead of relying on manual curation may ultimately be more efficient.

Progress on StRAP Objectives

The Life Cycle Analytics Project has made excellent progress as measured against the four objectives outlined in the 2016 StRAP. The project has clearly been "Building the Knowledge Infrastructure" and "advancing the understanding of relationships between chemical characteristics and potential impacts of use" through exploration of the relationships between chemical chemotypes and toxicity, as well as by developing the ability to predict functional uses and exposure to chemicals based on chemical characteristics and other data. This project area has also developed very important tools that will greatly facilitate "Chemical Evaluation", most notably including CPDat and the Chemistry Dashboard. The project has also contributed significantly to "Complex Systems Understanding" through the LC-HEM and their approaches to evaluating exposure throughout the lifecycle and ecotoxicity. Finally, the project area is clearly showing an ability to "Translate and Actively Deliver", and is already showing the ability to predict the toxicity of emerging materials and products. In summary, in the short space of one year, the project area has not only attained its short-term objectives, but has also made considerable progress toward its long-term objectives.

Recommendations

Recommendation 1.8: Periodic updates of underlying databases and checking against real-world exposure measurements will be essential for keeping this strong work relevant and useful for risk-based decision making.

Recommendation 1.9: Future efforts should focus on end-of-life aspects of chemical use.

Recommendation 1.10: Development of a data platform for emerging nanomaterials should be coordinated with a view to compatibility and functionality of other databases such as CompTox.

Charge Question 2. Integration

Based on prior feedback from this Subcommittee, over the past year, CSS has focused on further integrating the program within and between projects. Please comment on the progress. Is the integration approach right? Are there other areas that should be enriched?

Solutions-based Translation and Knowledge Delivery

Paloma Beamer, Jennifer McPartland

Solutions-based translation and knowledge delivery represents one of the four CSS research topic areas. The goal of this topic area is to demonstrate application of CSS science and tools to anticipate, minimize, and solve environmental health problems. There are three research projects under this topic area: (1) promotion of web-based tools, data, and applications focused on tailored solutions to support chemical safety evaluations and related decisions; (2) response to short-term high-priority science needs for CSS partners; and (3) allowance for active and strategic engagement of the stakeholder community.

Overall the Committee found that CSS has made significant progress in developing an assortment of web-based interfaces for CSS products, in engaging with agency partners to meet program and regional office needs, and in leveraging STAR grants to expand the scientific capacity of the program. Opportunity for improvement exists with regard to increasing stakeholder engagement and reconfiguring STAR grant RFAs. CSS is encouraged to develop a strategic plan for how to best balance available resources for collaboration and training on CSS products in the near- and long-term with both agency partners and external stakeholders.

Research Project Area 1: Promotion of web-based tools, data, and applications focused on tailored solutions to support chemical safety evaluations and related decisions

CSS Dashboards and Databases

Significant accomplishments have occurred in the past year in the design and development of various CSS chemical evaluation dashboards and databases including the CompTox Dashboard, ECOTOXicology Knowledgebase (ECOTOX), and RapidTox dashboard. The majority of these CSS products are publicly available online (e.g., CompTox dashboard, ECOTOX) with others on track to follow (RapidTox dashboard)—a critical feature of CSS products for which the program should be highly commended. Additionally, these platforms were designed to allow internal EPA partners, who must protect confidential business information, to download them onto their own servers while still maintaining automated updating of information and data sources.

CompTox Chemistry Dashboard

The CompTox Chemistry Dashboard, which is publicly available, contains a wealth of information on >720,000 chemicals and offers users an easy-to-use interface to access multiple sets of chemical and chemical-biology related data. This CompTox dashboard is likely to become a signature global product of CSS.

Key features and accomplishments of the CompTox dashboard include:

- Hyperlinks to several important information sources and databases within and outside EPA, with easy downloading capabilities in multiple formats. Links to external databases have been designed for automated, continuous updates, with only a few data sets that need to be manually updated.

- Significant work was accomplished in deleting outdated CAS numbers, which for several other databases, creates a significant problem in obtaining the right chemical information on various searches. This was a monumental task and speaks to the quality of effort put into developing the product.
- Information from the Chemicals and Products Database and RapidTox will be available via the CompTox dashboard and as stand-alone products. The modular design and links across CSS tools and databases is powerful, allowing users to bring diverse datasets together and enabling CSS to update information and products "systems-wide" in an efficient and uniform manner.

ECOTOX Knowledgebase

ECOTOX is an impressive database containing, for any given chemical, a plethora of rapidly retrievable, curated ecotoxicology data from the scientific literature. This effort could also improve read across species applications and evaluations of hazards of recently identify environmental and emerging chemicals. There are a few activities (some currently at least discussed or being considered) that would greatly strengthen this tool and make it more effective to use by partners. Specifically, efforts should be made to connect ECOTOX to the CompTox dashboard. This was mentioned as an effort going into the future, but the committee suggests that this activity be a priority for CSS. ECOTOX should also be hyperlinked to PubChem independently of, or through, the CompTox dashboard to provide additional, easy access to other chemical information.

Linkage between tools and software integration

There has been significant progress in linking different datasets and tools developed across the CSS program. With so many new tools being developed, graphics should be created to illustrate the linkages between the various tools in order to help CSS partners and stakeholders to understand and navigate these linkages. For example, as part of the LCA presentation, the Subcommittee was shown a slide "Software Integration" (slide 4 in Dr. Stevens' presentation). The slide was useful in showing the relationship among several LCA products. Expanding the graphic for to all CSS products would help users navigate among them.

Research Project Area 2: Response to short-term high-priority science needs for CSS partners

In response to concerns from last year it is clear that CSS is collaborating more with its partners to address key needs in the regulatory process. CSS researchers are excited and enthusiastic, and can clearly articulate why their projects are necessary and how they will help agency partners address bottlenecks that limit their ability to effectively manage chemical risks.

The BOSC Subcommittee heard from several EPA partners on how CSS products are being employed to identify and address short-term, high-priority science needs. Remarks from EPA regional and program offices clearly demonstrate that the CSS research program has engaged in a tremendous amount of outreach to them which has led to a handful of specific collaborative projects to meet real-world partner needs. This included assigning a CSS scientist to work on-site with partners to better understand their needs and demonstrate how the tools being developed can help the partners meet their regulatory responsibilities. A few highlights of such projects include:

- The Office of Pollution Prevention and Toxics (OPPT) shared a particularly timely and exciting pilot activity involving CSS products. The recently enacted Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg Act) grants EPA new order authority to require the development of chemical test data for various agency activities mandated by the law (e.g., new chemical reviews,

chemical prioritization, and chemical safety assessments). OPPT shared that is preparing to use this new authority for the first time for a specific set of chemicals, and is using the opportunity to explore what information can be provided by CSS to support the use of the order authority. This pilot effort provides a real-world example of how CSS products may be leveraged to support EPA implementation of its statutes.

- The EPA Office of Pesticides enthusiastically discussed work with CSS to: (1) support the identification of candidate common mechanisms for groups of chemicals in cumulative risk assessment and (2) use the RapidTox dashboard to prioritize further assessment of pesticide inerts in response to a petition received by the agency.
- An EPA Region 5 representative working on the Great Lakes Research Initiative spoke to how CSS HTT tools are aiding in the rapid evaluation of Great Lakes water samples that represent real-world mixtures of environmental chemicals.
- The Superfund program has been working with CSS to utilize RapidTox. This tool directly addresses their need to rapidly identify data for the vast number of poorly studied chemicals that are identified at sites.
- The Endocrine Disruptor Screening Program and the Office of Water expressed enthusiasm about the potential for CSS tools to help them more efficiently prioritize chemicals for further assessment and consideration. The Endocrine Disruptor Program has been meeting with CSS workgroups every week.
- Regions 2, 8 and 10 enthusiastically acknowledged efforts by CSS to engage with regional office scientists to better understand their information needs and in turn develop or modify CSS tools to support the work of regional offices.

The examples highlighted above showcase the breadth of agency needs to which CSS products can contribute. Summaries however were high-level and it would be useful for BOSC Subcommittee members to receive a more detailed assessment of these collaborations that would describe: (1) what was the need or problem addressed; (2) which and how CSS products were employed to address the problem/need; (3) characterization of the nature of the collaboration between CSS and EPA partners; (4) how, if at all, project outcomes informed CSS products (e.g., positive-feedback loop); (5) whether the agency partner found the collaboration to be valuable and, if so, how; and (6) lessons learned scientifically, logistically, and otherwise through the collaboration.

Utilization of CSS developed tools and advice in EPA regional and program offices should be documented and included among metrics of success. To facilitate the gathering of this information, for example, CSS could request that its partners use the specific tool names in their reports and related materials when those tools are used. Additionally, identifying methods to evaluate the impact of CSS products in various regulatory activities, could help showcase the utility of CSS and increase the rate at which partners adopt CSS tools. CSS impact metrics should be developed to measure how CSS products help to make better and more informed decisions.

More broadly, it appears that CSS is pursuing two approaches for engagement with EPA partners, one in which there is active involvement by CSS scientists to jointly conduct an evaluation with its agency partners, and a second to develop completely user-friendly dashboards that can be applied by a partner or stakeholder. Both efforts are commendable but require significant resources that may not be available to enable both to be accomplished within the fiscal limitations that currently exist. CSS should continue to focus on assisting internal partners to address their needs. This will assure that the approach and assumptions used are done correctly, and help navigate concerns that may exist in replacing current methods that are used for exposure evaluation, hazard determination and risk assessment. It is also

valuable to continue to develop and make publicly accessible dashboards so that basic information can be accessed by partners and stakeholders with sufficient expertise. By doing so, EPA expands the internal and external user community using CSS products. Broadening the community of users of CSS products leverages investments made in the program; enables external, parallel exploration of the applicability of CSS products; and ultimately works to build confidence in the use of CSS products. The Subcommittee recognizes the personnel and fiscal challenges posed by pursuing active advisement and building user-friendly dashboards. CSS should scope what training needs are required and ideal in the near- and long-terms. The Subcommittee could provide feedback on such a plan to the extent it would be helpful.

In summary, it is essential to highlight that CSS has made great strides in developing collaborations with their partners. It will take time to develop these relationships and trust in the new tools and research coming out of CSS. However, the progress that has been made is truly astounding. By understanding the needs of their partners better, CSS research is more likely to be efficiently utilized in meeting the mission of the Agency.

Research Project Area 3: Active and Strategic Engagement with the Stakeholder Community

Over the past year there has been some progress toward stakeholder outreach and engagement. Stakeholders are defined as entities outside EPA and distinct from internal EPA partners. Aside from external research and collaborations through STAR grants, limited presentation and discussion specifically focused on stakeholder engagement. There was one poster on stakeholder engagement which showcased a newly developed CSS website aimed at capturing, characterizing, and tracking CSS research outputs (see discussion below). Aspects of stakeholder engagement arose in some discussions around CSS projects, in particular outreach to the broader basic research community in the development of AOPs and the AOPwiki.

Stakeholder engagement could be greatly enhanced through developing mechanisms of multi-way contact; documenting the feedback, uptake and impact of CSS tools from and on stakeholders; additional future STAR grants, and increased engagement with the public.

CSS Website to Track Research Outputs

The CSS research program has developed a website that showcases publications by CSS researchers (poster #23 - CSS: Measuring the Impact of EPA's Computational Toxicology Research). This is a useful step toward demonstrating the caliber and breadth of research ongoing at CSS. The site is well laid-out and uses highly innovative web features that allow viewers to easily identify and search across publications from individual CSS scientists. Citation frequency of CSS publications is also captured. Unfortunately, there are barriers to the impact of this project because of the current state of the IT infrastructure and website development policies that have prevented this website for being available to external stakeholders. The website could be enhanced to document the use of CSS tools by external stakeholders (e.g., listing of publications that used CSS products by individuals and groups external to EPA). This would provide a meaningful measure of CSS "impact" and acceptance by the broader research community.

STAR Grants

STAR grants provide invaluable opportunities for broader engagement with the scientific community and complement the CSS team's existing expertise. For example, there has been great progress in activities like the Virtual Tissues projects and biomonitoring of mixtures in pregnant women through partnerships with STAR grantees.

Resources permitting, CSS should develop additional STAR RFAs that fill gaps in CSS project areas and simultaneously forge collaborations with external researchers in fields for which CSS has expressed interest and value, but has yet to engage. For example, CSS is the EPA lead on the national program for the "Children's Environmental Health" roadmap. As such, CSS has a tremendous opportunity to be the leader in integrating data and findings from epidemiological studies into the development and evaluation of CSS products for chemical mixtures with specific relevance to children's health. Vast amounts of data collected as part of the EPA/NIEHS Children's Centers and the new ECHO and CHEAR initiatives will provide amazing resources and opportunities. CSS does not have the epidemiological or biostatistics expertise necessary to fully utilize these data for evaluating their tools. Further, CSS has had minimal success engaging the environmental epidemiology community despite attempts and acknowledged importance of the field to the work of CSS. An EPA STAR RFA targeted at integrating epidemiological data with CSS products could provide an opportunity to reach researchers in this field that could assist in evaluating CSS tools in relation to actual health outcomes documented in children.

More generally the STAR RFAs could benefit from being more focused. Some of the previous RFAs have been a compilation of several research areas, and therefore have less likelihood of actually addressing what might be needed by any one part of EPA. More focused STAR RFAs would aid in getting the appropriate researchers, rather than those who can address multiple research areas, to dedicate their creativity and develop tools that are better suited to addressing Agency needs. This would lead to more focused grant applications, rather than ones that are trying to address multiple research areas in one grant application.

Engaging the Public

CSS products have obvious importance to various EPA programs. In time, as comfort and confidence in the CSS program is more established, some form of lay-friendly, public-facing CSS information and products would be useful to help the public understand the significance of any exposure they might be experiencing. Through discussions with CSS researchers, it appears that some such activities have already occurred (e.g., webinars). In future presentations, it would be important to provide evidence of dissemination, such as interactions with advocacy organizations, professional scientific societies, impacted communities, and a digest of talks, webinars, meetings, and related forums with external stakeholders and the public. The Committee acknowledges, supports, and finds value in the various factsheets for public consumption that the CSS program has produced to date.

Recommendations

Recommendation 2.1: Build links with ongoing NIH-funded cohort studies to use biomonitoring information from those studies and provide toxicity pathway information to enhance those studies.

Recommendation 2.2: The ongoing work is rich in detail but the user of various elements could get lost in the details and not recognize how they all relate to one another. An interactive tool or a graphic would help users understand the relationships of the available sources of data.

Recommendation 2.3: Consider how to best balance available resources for collaboration and training on CSS products in the near- and long-term with both agency partners and external stakeholders, focusing on direct interactions to demonstrate how the tools can help partners meet their mission to protect the environment and public health.

Recommendation 2.4: Generate protocols for assessing the impacts of CSS research on EPA partners and external stakeholders including both researchers and the general public. This should include development of some metrics that would document success for each of the research project areas under this topic area.

Recommendation 2.5: Craft more focused STAR RFAs that address a particular project area need that would build collaborations between CSS and key external researchers, including investigators that may not traditionally work on environmental issues.

Summary List of Recommendations

Charge Question 1. Science

Are we doing the right research? Taking resource limitations into considerations, are there any significant scientific gaps?

Chemical Evaluation

- **Recommendation 1.1:** Articulate a unifying strategy for how transcriptomics and other data are being used in CSS to inform new assay development using the AOP framework.
- **Recommendation 1.2**: As appropriate, retire existing assays that may not add sufficient value to the program while bringing on board new assays that add important biological content to the hazard identification mission.
- **Recommendation 1.3:** Evaluate whether assays of single chemicals over- or under-predict the effects of combined exposures to mixtures.

Complex Systems Science

- **Recommendation 1.4:** Consider creating a pipeline of scientifically sound and accepted AOPs awaiting OECD endorsement.
- **Recommendation 1.5:** Continue to advance the science in virtual tissue modeling, including the STAR program, and look for points of entry to application while extending the approach to other organs as resources allow.
- **Recommendation 1.6:** Extend complex systems approaches into model organisms and intact systems to bridge the outstanding work done *in vitro* into read across species applications commensurate with AOP areas of focus for both ecological and human hazard identification.

- **Recommendation 1.7:** Continue focusing on engagement wherever possible to illustrate the power of applying systems science to risk assessment.

Lifecycle Analytics Project

- **Recommendation 1.8:** Periodic updates of underlying databases and checking against real-world exposure measurements will be essential for keeping this strong work relevant and useful for risk-based decision making.
- **Recommendation 1.9:** Future efforts should consider end-of-life aspects of chemical use.
- **Recommendation 1.10**: Development of a data platform for emerging nanomaterials should be coordinated with a view to compatibility and functionality of other databases such as CompTox.

Charge Question 2. Integration

Based on prior feedback from this Subcommittee, over the past year, CSS has focused on further integrating the program within and between projects. Please comment on the progress. Is the integration approach right? Are there other areas that should be enriched?

- **Recommendation 2.1:** Build links with ongoing NIH-funded cohort studies to use biomonitoring information from those studies and provide toxicity pathway information to enhance those studies.
- **Recommendation 2.2:** The ongoing work is rich in detail but the user of various elements could get lost in the details and not recognize how they all relate to one another. It would be helpful for EPA to develop an interactive tool or graphic that would help users understand the relationships of the available sources of data.
- **Recommendation 2.3:** Consider how to best balance available resources for collaboration and training on CSS products in the near- and long-term with both agency partners and external stakeholders, focusing on direct interactions to demonstrate how the tools can help partners meet their mission to protect the environment and public health.
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- **Recommendation 2.5:** Craft more focused STAR RFAs that address a particular project area need that would build collaborations between CSS and key external researchers, including investigators that may not traditionally work on environmental issues.

APPENDIX A: MEETING AGENDA

Time	
8:00 - 8:30	*R*
8:30 – 8:45	W
8:45 – 9:00	D
9:00 – 9:15	O
9:15 – 9:30	O
9:30 – 9:45	R
9:45 – 10:00	*B*
	CSS Chemi
10:00 – 10:20	A
10:20 – 10:40	H
10:40 – 11:00	R
11:00 – 11:20	D
11:20 – 11:40	V
11:40 – 12:30	S
12:30 – 1:30	*L*
1:30 – 4:30	P
1:30 -- 4:30	C S
4:30 – 5:00	S
5:00 –5:45	S
5:45 – 6:00	W

Thursday, November 17, 2016 Main Meeting Room A-015; RTP Overflow Rooms: A-134 Call-in: 1-866-299-3188, passcode: 202-564-6604# Webinar: https://epawebconferencing.acms.com/cssbosc2016/		
Time	**Topic**	**Presenter**
8:30 – 8:40	Welcome and Review of Day 1	Ponisseril Somasundaran Gina Solomon
8:40 – 8:45	Overview of Day 2	Tina Bahadori
CSS Life Cycle Analytics Topic Area Research Project Deep Dive		
8:45– 9:05	Sustainable Chemistry	Caroline Stevens/Todd Martin
9:05-9:25	Life-Cycle Human Exposure Modeling	Jane Bare/Paul Price
9:25 – 9:45	Emerging Materials	Kim Rogers/Michael Hughes
9:45 – 10:05	*Break*	
10:05– 10:25	Ecological Modeling	Matt Etterson/Tom Purucker
10:25– 11:00	Subcommittee Discussion and Deliberation	
EPA Program and Regional Offices Engagement of CSS		
11:00 – 12:30	Program and Regional Offices Perspectives on CSS	Participants: • Carole Braverman, Region 5 & GLRI (by phone/webinar) • Betsy Behl, Office of Water • Marie O'shea, Region 2 • Tala Henry, OCSPP Office of Pollution Prevention and Toxics • Anna Lowit, OCSPP Office of Pesticide Programs • Stan Barone, OCSPP Office of Science Coordination and Policy • Bruce Duncan, Region 10 • Kathleen Raffaele, Office of Land and Emergency Management • Wendy O'Brien, Region 8
12:30 – 1:30	*Lunch*	
CSS Poster Session and Genius Bars		
1:30 – 4:30	Poster Session #2: Atrium B	
1:30 – 4:30	Concurrent Genius Bars; Classroom C114 RapidTox; CPDat; Chemistry Dashboard	CSS Scientists
4:30 – 5:00	Subcommittee Discussion and Deliberation	Subcommittee
5:00 – 5:30	Subcommittee Discussion of Charge Questions	Subcommittee
5:30 – 5:45	Public Comments (if any)	
5:45 – 6:00	Subcommittee Wrap-up and Adjourn	Ponisseril Somasundaran Gina Solomon

Friday, November 18, 2016 Main Meeting Room A-015 Call-in: 1-866-299-3188, passcode: 202-564-6604# Webinar: https://epawebconferencing.acms.com/cssbosc2016/		
Time	**Topic**	**Presenter**
8:30 – 8:45	Welcome and Review of Day 1 and 2	Ponisseril Somasundaran Gina Solomon
8:45 – 9:15	Update on Human Health Risk Assessment (HHRA) National Research Program	John Vandenberg, HHRA NPD
Subcommittee Deliberations on CSS Charge Questions and Report Writing		
9:15 – 10:00	Subcommittee group discussion of CSS preliminary findings and recommendations	Subcommittee
10:00 – 12:00	Subcommittee breakout group by CSS charge questions -discussion and writing (includes a break)	Subcommittee Breakout Groups
12:00 – 1:00	*Lunch*	
1:00-3:00	Discussion of outstanding issues, review of draft report, review of timeline and assignment of follow up activities.	Subcommittee Breakout Group Leads
3:00 - 3:30	Wrap Up and Adjourn	Ponisseril Somasundaran Gina Solomon