U.S. Environmental Protection Agency (EPA)
Board of Scientific Counselors (BOSC) Subcommittee for
Chemical Safety for Sustainability (CSS) and Human Health Risk Assessment (HHRA)

Face-to-Face Meeting Minutes

October 6–8, 2015

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Date and Time: October 6, 2015, 8:00 a.m. to 5:30 p.m.; October 7, 2015, 8:30 a.m. to 5:30 p.m.; October 8, 2015, 8:30 a.m. to 3:30 p.m.

Location: EPA Campus – C112, 109 T.W. Alexander Drive, Research Triangle Park (RTP), North Carolina

Meeting Minutes

Provided below is a list of the presentations and discussions that took place during the meeting with hyperlinked page numbers. The minutes follow. The agenda is provided in Appendix A, and the participants are listed in Appendix B. Charge questions are provided in Appendix C.

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Tuesday, October 6, 2015

The meeting generally followed the issues and timing as presented in the agenda attached to this meeting summary.

Welcome and Introductions

Dr. Ponisseril Somasundaran, Chair

Ms. Megan Fleming, Designated Federal Officer (DFO) of the BOSC CSS and HHRA subcommittee, welcomed everyone to the meeting and turned the meeting over to Dr. Somasundaran, chair of the subcommittee, and Dr. Gina Solomon, vice-chair of the subcommittee. Dr. Somasundaran requested that each subcommittee member introduce themselves and began by saying he is a Professor at Columbia University in the area of green chemistry, nanoparticles, and toxicity. He has experience working in the area of wastewater processing remediation, specifically with microbial interactions with nanoparticles and is a member of the National Academy of Engineering of US and other countries. Dr. Solomon, vice-chair of the subcommittee, is the Deputy Secretary for Science and Health in the Office of the Secretary at California EPA (CalEPA), and she advises the Secretary of CalEPA. She is also a Clinical Professor in the Department of Occupational and Environmental Medicine at the University of California at San Francisco, has served on the EPA Science Advisory Board (SAB) for a number of years where she participated in previous reviews of this program, and served on the National Academy Committees for the Tox21 and Exposure21 efforts. Ms. Fleming stated that she will serve as the subcommittee DFO and will elaborate on her role in the subcommittee during the next agenda item. Dr. Jerzy Leszczynski is a Professor at Jackson State University and is a professional chemist. His expertise is in computational chemistry where he examines different properties and toxicities of materials. Dr. Jennifer McPartland is a Senior Scientist at the Environmental Defense Fund. She is a molecular biologist by training but now works on cross-cutting topics that include policy, corporate engagement, and science. Dr. Jim Stevens is a Distinguished Research Fellow at Eli Lilly and has over 25 years of experience conducting technology development as it pertains to risk assessment, mechanistic toxicology, application of gene expression technology, and other technologies for risk assessments. Dr. Rebecca Klaper is a Professor at the School of Freshwater Sciences at the University of Wisconsin at Milwaukee. Her research is focused on the impact of emerging contaminants on freshwater organisms, including anything from pharmaceutical to personal care products. She is also part of the Center for Sustainable Nanotechnology, funded by the National Science Foundation, which aims to redesign nanoparticles to make them more sustainable. Dr. Paloma Beamer is an Associate Professor at the College of Public Health and Chemical Engineering at the University of Arizona. Her research is in exposure science and risk assessment with a focus on children's health, as well as Latino and African American health in rural populations. Dr. Dale Johnson is an Adjunct Professor at both the University of California at Berkeley and the University of Michigan where he started the computational toxicology programs at both universities. He is also the CEO of several startup companies involved in biotechnology, pharmaceutical, and environmental issues and is a member of first Green Urban Science Council in California. Dr. Katrina Waters is the Director of the Biological Science Division at Pacific Northwest National Laboratories. Her background is in computational toxicology, specifically microarray and high-

throughput screening data analysis. Dr. Donna Vorhees is a Senior Scientist for the Science and Health Institute in Boston where she is working on oil and gas research and development. She has over 20 years of experience working on human health risk assessment exposures and she is also an Adjunct Assistant Professor in the Department of Environmental Health at Boston University where she teaches risk assessment methods.

Dr. Somasundaran asked for comments on the agenda, and, hearing none, he explained that the subcommittee will examine the documents prepared for the meeting to address the science issues posed in the charge questions and identify any gaps. He notified subcommittee members that he would ask for volunteers to take notes and write sections of the report during the meeting and then turned the meeting over to vice chair Dr. Solomon to proceed with the opening remarks.

Opening Remarks
Dr. Gina Solomon, Vice Chair

Dr. Solomon explained that the CSS and HHRA subcommittee is part of a set of BOSC subcommittees that are all meeting this fall. The Executive Committee will meet in December to review and pull together all the subcommittee reports into one document. She expressed that, in some ways, this subcommittee has the most exciting task, because they are reviewing two programs, one of which is very cutting-edge and the other cuts across many of EPA's programs. However, the subcommittee's work could be considered the most challenging task because the review is so comprehensive, and the subcommittee is the smallest of all the BOSC subcommittees and has the least amount of time to complete their report. Dr. Solomon added that, with those things in mind, she hoped to keep the subcommittee focused on the task at hand during the meeting, so that the subcommittee has a clear sense of how to respond their charge questions and complete as much writing as possible by the end of the meeting. She asked that subcommittee members keep the charge questions and how to respond to them in mind as they listen to and discuss presentations and topics presented during the meeting. She also forewarned the members that she may ask members to write a paragraph on a topic of the report as they make comments and ask questions throughout the meeting. Dr. Solomon suggested the subcommittee begin writing responses to the charge questions today and tomorrow and think about recommendations based on their areas of expertise. The subcommittee will be reviewing the Strategic Research Action Plans (StRAPs) and will discuss if EPA is fulfilling those objectives contained therein. Dr. Solomon thanked the subcommittee members for agreeing to take part in this effort. Dr. Somasundaran turned the meeting over to Ms. Fleming to review the Federal Advisory Committee Act (FACA) rules.

DFO Welcome and FACA Rules
Ms. Megan Fleming, DFO

Ms. Fleming provided the background material that the subcommittee's objective is to provide targeted advice on project research articulated in the StRAP for 2016–2019. Throughout the next few years, EPA plans to re-engage the subcommittee to obtain input and recommendations regarding how the program is developing and how well the program research portfolio is addressing the research outlined in out StRAP. As the subcommittee chair and vice chair articulated, the goal for this meeting is to generate a report with advice and recommendations for

EPA by November 17, 2015. This deadline will allow the BOSC Executive Committee sufficient time to conduct a meaningful review of the report in preparation for their meeting schedule for December 8, 2015.

Ms. Fleming explained that the BOSC is a federal advisory committee established and operated under the authority of the FACA. As DFO for the subcommittee, she is responsible for ensuring that all BOSC activities comply with FACA, which requires that all meetings are open to the public, with all substantive subcommittee and EPA discussion held in an open forum, and include opportunity for public comment. The meeting minutes, being taken by EPA's contractor, record all deliberations and will be made available to public after being certified by the chair and within 90 days after meeting commencement. An announcement of the meeting is required to be published in the *Federal Register* at least 15 days prior to any meeting, and EPA also established notice of the public docket for this meeting. Ms. Fleming added that the meeting notice, public docket, and all materials for this meeting can be accessed at regulations.gov and are also available on EPA's BOSC website. She reminded the audience that all meetings involving substantive issues—whether in person, by phone, or by email—are open to the public. This applied to all group communications that include at least half of the subcommittee and Ms. Fleming asked that subcommittee members keep this in mind when sending emails. As the liaison between the subcommittee and EPA, Ms. Fleming (or any DFO) is required to attend all meetings and ensure that they are announced in the *Federal Register*. Furthermore, Ms. Fleming and EPA officials worked to ensure that all subcommittee member ethics requirements were satisfied and asked members to notify her if any potential conflicts of interest arise during subcommittee discussions, particularly if a topic pertains to any member's area of research.

Ms. Fleming noted that no public comments have been submitted at this time and asked that any member of the public that wishes to make a comment identify themselves so she can ensure that their comment is made during the public comment period on the agenda, scheduled for the afternoon on Day 2 of the meeting. She added that comments will be limited to three minutes.

Ms. Fleming reviewed the responsibilities of the subcommittee chair, including running the public meeting according to the pre-approved agenda, determine how to manage any deviations from the agenda and if questions are inappropriate, ensure that subcommittee and audience members identify themselves when speaking, and ensure the meeting stays on time. She reminded everyone that it is important to identify themselves and speak into the microphones for the meeting notes and that the meeting was recorded for note purposes only. Ms. Fleming added that all ten subcommittee members expected to attend the meeting were present, one subcommittee member, Dr. Clifford Weisel from Rutgers University would be joining the meeting tomorrow, and three subcommittee members, Dr. Mark Weisner from Duke University, Dr. Kyle Kolaja from Cellular Dynamics International, and Dr. Chris Gennings from Mt Sinai Hospital School of Medicine were unable to attend the meeting due to prior engagements. Ms. Fleming then turned the meeting over to the two National Program Directors (NPDs) for the CSS and HHRA research programs.

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Overview of Agenda, Structure of Joint CSS-HHRA Programmatic Review, and Discussion of Materials Provided
Dr. Tina Bahadori, CSS NPD & Dr. John Vandenberg, HHRA NPD

Dr. Bahadori explained that the BOSC EC meeting in December will be attended by the subcommittee chairs and vice-chairs. She and Dr. John Vandenberg were the EPA team members who led this part of the meeting discussion, but many of the EPA team members were either present or following discussion on the webinar. Dr. Bahadori introduced Dr. Elaine Hubal, who is the Deputy NPD of the CSS research program. Dr. John Vandenberg introduced Dr. Annie Jarabek, who is the Deputy NPD of the HHRA research program, and noted that there were a number of people participating on the webinar who assisted in preparing the meeting materials.

Dr. Bahadori and Dr. Vandenberg walked through the meeting materials. Dr. Bahadori noted that the binder circulated to members primarily consisted of materials for the CSS program, and a comparable binder for the HHRA program would be disseminated later. She explained that the joint CSS-HHRA meeting will be challenging to navigate. The HHRA program undergoes a significant review process for a number of different products, Dr. Vandenberg further explained, and is a crosscutting program. He said it will be tempting to the subcommittee to delve deeply into the entirety of the program, but it is important to remember that section of the program the subcommittee will be reviewing is a small slice of a fairly complex program. Dr. Bahadori reinforced that, for this meeting, subcommittee members should focus on the section of the HHRA program that is the leading edge of research in the field of human health risk assessment, which is the component that EPA asked the subcommittee to review.

Dr. Bahadori referenced the USB drives provided to the subcommittee members before the meeting and provided an overview of the materials included in the binder. Those materials included the charge questions, the StRAPs for both programs, CSS Project Charters which are the high level descriptions of the projects specific to the program, and initial joint review by the SAB and BOSC of the CSS and HHRA programs. She explained that it is unusual for BOSC to meet this early in the StRAP process, as EPA is just launching the 2016–19 review, and there is not a lot of implementation information available. However, EPA would like the subcommittee members to become familiar with the program and the StRAP early on to help ground the process in this upfront knowledge, thus facilitating the best feedback and recommendations possible. Dr. Bahadori added that early feedback will allow the Office of Research and Development's (ORD's) lab and centers leadership teams, who implement the research projects, to strategically manage the research projects and bring recommendations to their teams and make adjustments early on the process. She said that ORD hopes to engage the subcommittee over the next few years in a deeper and more intimate manner.

Dr. Bahadori explained that there will be a session on Day 2 in the afternoon from 3:45 – 5:45 when subcommittee members will hear from program managers and regional partners and have an opportunity to engage in discussion with them. This will inform the subcommittee's assessment of how effective the program has been in regards to engaging the portions of EPA that the program is tasked with providing scientific support to and how effective and responsive the program has been in soliciting their interests and guidance. Dr. Bahadori noted that they

provided biographies of those panel members that span the Agency to give the subcommittee a sense of the seniority and level of engagement of the panel and expressed her gratitude that many of EPA program representatives who were willing to travel to RTP or join remotely to respond to the subcommittee's questions. In addition, Dr. Bahadori noted the two-page CSS factsheet was provided to the subcommittee, but the StRAP provided much more detailed information. They also provided an organizational list of ORD that summarized the information that Deputy Assistant Administrator of Science, Dr. Robert Kavlock, provided in his overview of ORD. She asked that subcommittees ask for clarification if there is confusion about any of these organizational structures. Dr. Bahadori reviewed that the ORD overviews were also provided to the subcommittee in a webinar.

Additional materials included in the materials provided are her and Dr. Vandenberg's biosketches and the concurrence document on the design of the actual research projects for the fiscal year of 2016 under CSS. In the concurrence document, a table that highlights what the majority of the projects will be was included in the handout. Dr. Bahadori added the caveat that ORD's products are what they have committed themselves to developing but, because the projects entail a much wider scope, there will likely be many more products delivered than the number of products promised. For example, ORD has promised 10 products but will likely deliver closer to 100 products. Dr. Bahadori's slides for the entire meeting were also included that contained shorthand notes that will assist in working through the StRAPs. Dr. Bahadori added that there will be a poster session, demonstrations or what CSS called the Genius Bar, and HHRS software demonstrations that are described in the meeting packet.

Dr. Vandenberg noted that Dr. Bahadori alluded to the complicated intersection of the CSS and HHRA programs, and he added that much of HHRA is not being evaluated by this subcommittee. HHRA was challenged with providing enough information to the subcommittee for its review without skewing it, because the bulk of the effort should be focused on CSS. Dr. Vandenberg explained that the subcommittee received that StRAP in advance but will be provided with HHRA's presentation materials, project descriptions, and poster and demonstration abstracts. He explained that HHRA will provide targeted presentations on areas related to the program's community support, including rapid response and cumulative risk, work on improving the scientific basis for advancing hazard identifications, dose-response, and evaluation of emerging science that closely links with the CSS program, and risk assessment support and training activities, including the substantial behind the scenes effort of risk assessments such as the tremendous databases, systems, and models used and efforts to provide transparency to public. Dr. Vandenberg reiterated Dr. Bahadori's comments about the poster session and regional program office partner discussion will provide a great opportunity for the subcommittee to receive input that will help their evaluation of the programs and their responses to the charge questions. Dr. Vandenberg added that, although he would be happy to address any questions about Integrated Science Assessments (ISAs) or the Integrated Risk Information System (IRIS), but that is not the point of this review. Dr. Vandenberg then turned the meeting back over to the subcommittee chair and vice chair.

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Review and Assignment of Charge Questions

Dr. Ponisseril Somasundaran and Dr. Gina Solomon

Dr. Somasundaran noted that the meeting was ahead of schedule and reviewed the charge questions that were distributed prior to the meeting. He explained that SAB assessed the science that EPA should be doing, and the BOSC subcommittee is tasked with assessing if the science has been done correctly.

Dr. Somasundaran introduced the three general Charge Questions.

BOSC General Charge Questions

Charge Question 1: Given the research objectives articulated in the Strategic Research Action Plan (StRAP), are the topics and project areas planned and organized appropriately to make good progress on these objectives in the 2016-2019 time frame?

Charge Question 2: How effective are the approaches for involving the EPA partners in the problem formulation stage of research planning?

Charge Question 3: How well does the program respond to the needs of EPA partners (program office and regional).

Dr. Solomon noted that these questions were the three general charge questions that the subcommittee will be asked to respond to for both CSS and HHRA over the next few days. They are fairly broad so the subcommittee could draft responses in a number of ways, but the general theme of the questions that the subcommittee will need to determine is whether the programs are moving in the direction to achieve the objectives set out by 2016–2019 StRAP. She suggested that subcommittee members refer to the StRAP, specifically the executive summaries, throughout the meeting to help make this determination. She added that there will also be specific charge questions that are program specific that Dr. Somasundaran will review. Dr. Solomon referred back to previous discussion about assigning members to take the lead on certain sections but raised the issue that members have expertise that will cut across charge questions so team flexibility will most likely be required. She asked members to think about which charge question they could contribute the most to give their expertise. Dr. Somasundaran agreed that the StRAP executive summary is very well done and that the first 10 pages of the document covers almost everything.

Dr. Somasundaran introduced the specific subcommittee charge questions.

Subcommittee-specific Charge Questions

CSS Charge Question 4: Please provide input on the scope and implementation for 2016-2019 in the following topic areas: a. Complex Systems Science, b. Lifecycle Analytics, c. Chemical Evaluation.

CSS Charge Question 5: Please provide input on opportunities and approaches for fit-for-purpose translation and knowledge delivery.

HHRA Charge Question 6: Please comment on the research dimensions of the HHRA program and, in particular, the proposed approaches for characterization of new data and computational methods to improve confidence and build capacity for their application in the context of risk assessment.

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Dr. Solomon asked subcommittee members if they had any questions about the charge questions and added that the subcommittee is also permitted to provide any general thoughts or overarching recommendations in addition to the charge questions.

Dr. Johnson asked that, if the subcommittee does not agree that the program is carrying out the science correctly or in a way that the subcommittee did not envision for the StRAP, if the subcommittee should then also provide a new way for conducting the science. Dr. Somasundaran responded that there should be consensus among subcommittee members if there is something missing before it is included in the report. Dr. Bahadori added that ORD would greatly value any feedback along the lines of information or implementations efforts that are missing. She added that specific examples would be most helpful, as there are often reasons as to why something is missing. However, it may be that ORD has not thought of everything, so CSS would absolutely value any feedback on gaps, specifically specific and detailed feedback.

Dr. McPartland asked for clarification on what was meant by EPA "partners" in both the general and subcommittee specific charge questions. Dr. Bahadori clarified that, for this review, the partners refer to EPA's program offices and regional partners, who are ORD's primary "clients." However, when ORD describes the broad community of science, they could be referring to a broader audience. Dr. Vandenberg added that the term "stakeholders" is sometimes used, which includes organizations outside of the Agency. However, for the purpose of the charge questions, "partners" refers to EPA's program and regional offices.

Dr. Somasundaran asked for volunteers to take notes and write sections on specific charges questions. Dr. Solomon suggested that these writing assignments be made as further discussions are had. Dr. Bahadori suggested that writing assignments can also be broken up by topic area or group of expertise rather than charge question. Dr. McPartland volunteered to take notes at this point, and members agreed that they can discuss writing assignments later. Dr. Stevens also volunteered to take notes and noted that he was struck by the fact that charge question 1 and 6 appeared to be questions for the entire BOSC while the other questions that address the scope of the research projects appear to be more specific to areas of expertise. For example, charge question 6 appears to be requesting an aggregation of all comments into an overarching recommendation. Dr. Solomon agreed, adding that this question was really focused on risk assessment. She suggested that people more familiar with this topic work to address that question. Dr. Bahadori reiterated her point that the scope of this review is a small effort of HHRA and does not include IRIS, so this question should be addressed by the subcommittee as whole and not just several committee members.

Dr. Stevens raised the point that two of the charge questions ask about ORD's relationships with partners and two questions are specific to technology and risk assessment. Dr. Solomon responded that she would like subcommittee input on how to tackle these charge questions. She provided the options that the subcommittee could split up the questions or address them as a group. She noted that the group is small enough that it would be feasible to tackle the questions as a group, but she was leaning towards splitting them up. Dr. Somasundaran suggested assigning a lead for each charge question. Dr. Stevens followed up to Dr. Somasundaran's comment by asking if the exact assignments could be shuffled later in the day, after review of the StRAPs' map to these projects, and subcommittee members agreed. Dr. Solomon also agreed and noted that the main purpose for this agenda item was to focus on and think about the charge

questions as a group. She reiterated that she would like the subcommittee to keep the charge questions and possible responses in mind and to actively listen to the meeting presentations.

Dr. McPartland asked when subcommittee members should expect to receipt meeting minutes. Ms. Fleming responded that the subcommittee will be emailed an overall summary of notes from Day 1 of the meeting tonight and be provided a printed version tomorrow before Day 2 of the meeting commences.

CSS Program Purpose and Design (General Charge Question 1)
EPA Overview: Dr. Tina Bahadori
Subcommittee Discussion: Subcommittee

Dr. Bahadori explained that ORD is interested in feedback on if they are doing the correct science to meet the StRAP's objectives. She explained that she would present on the general overview of EPA, provide a high level overview of the CSS research program, a more detailed review of the research topics and projects in the StRAP, the cross-program integration, the strategic partnerships and partner engagement, and the translation on knowledge delivery. She added that her slides provide a lot of information but she will leave plenty of time for discussion and that the full set of slides were available in subcommittee member's binders. Dr. Bahadori added that her hope was after her presentation and the poster session is for the subcommittee to have a good grasp on how ORD engages partners and conducts a few other activities.

Dr. Bahadori began by restating that EPA's partners consist of EPA program and regional offices and ORD provides the science that the Agency uses. The program offices make the national decisions, and Dr. Bahadori introduced Dr. Kathleen Raffaele, who represented the Office of Solid Waste and Emergency Response (OSWER), and Dr. Santhini Ramasamy, who represented the Office of Water (OW), who were present at the meeting. The decisions of the Agency are implemented on the regional side, and several representatives are on the webinar and will join the meeting later that day and the next.

Dr. Bahadori explained how EPA was organized from ORD's standpoint. The Office of Chemical Safety and Pollution Prevention (OCSPP) is the main office that ORD CSS supports, but because many issues in the chemical space are driven by the OW, OSWER, and by regional offices, there is a significant amount of interaction between offices, including the Office of Children's Health Protection (OCHP).

ORD was traditionally organized by its national research laboratories and centers until three years ago when it was reorganized. Dr. Bahadori introduced Dr. Russell Thomas, the Director of the National Center for Computations Toxicology; Dr. Ron Hines, the Associate Director of Health and Environmental Effects Lab; and Dr. Andrew Gillespie, from the Exposure Research Lab, who were present at the meeting. The National Research Labs and Centers are where the research is carried out.

She explained she and Dr. Vandenberg are one of six NPDs who operate at the strategic interface between the program and regional offices, including the Office of the Administrator, to help them determine their research needs, visualize their strategic direction, help allocate funds to support the research vision, and work with the lab and center leadership teams to implement their research. ORD works within a matrix, with labs and centers on the horizontal axis and the NPDs

on the vertical axis. At the intersection are staff who serve as Matrix Interfaces, employees whose responsibilities Dr. Bahadori will describe later in her presentation.

The new EPA strategic goals are described in the 2014 StRAP that covers the period from fiscal years 2014 to 2018. Several research priorities are outlined in the StRAP, including the priority to ensure the safety of chemicals and pollution prevention, protecting America's waters, and cleaning up communities. These priorities inform ORD's decisions regarding how to organize a research program. Dr. Bahadori explained that CSS is primarily aligned with ensuring the safety of chemicals, regardless of the space they are in.

Dr. Bahadori explained the process that she, Dr. Hubal, and the partner labs and centers used to develop the StRAP. The CSS program operates at the interface between understanding that chemicals are essential to modern life, recognizing the current difficulty in innovation and determining the transformative value of chemicals, considering the economic value, and the challenge of ensuring chemical safety of environmental and public health. Thus, a large part of the CSS program is geared towards chemical safety evaluations and informing safety decisions, including risk assessments, while another large part of the program is geared towards transformative innovation. Dr. Bahadori explained that multiple EPA programs and regions must make risk-based decisions for addressing chemicals with often inadequate or non-existent information about their safety. EPA would like to demand more testing information and exposure data on chemicals, but it is not feasible to generate enough test data on the all the chemicals already on the market with the resources available. To provide perspective, Dr. Bahadori explained that there are 80,000 chemicals in the Toxic Substances Control Act (TSCA) inventory and that list is growing. Of those chemical, 15,000 to 30,000 are used regularly but only 300 to 500 have been tested for their safety. Current toxicity methods are not adequate to evaluate the volume of chemicals, so CSS is thinking of approaches that will allow better understanding of the safety of these chemicals that allow state agencies, regional partners, industry, and stakeholder communities can use that information to evaluate the safety decisions that they need to make.

Dr. Bahadori also explained that traditional toxicology models are based on high dose toxicity testing, but these fail to capture the chronic, low dose exposures. She noted that the relevance and validity of traditional toxicity testing must be revisited for these types of exposures. EPA wrote a white paper which used case studies to develop guidance for low dose exposures. The issue of low dose exposures is complicated further by the consideration of cumulative exposures, specifically assessing levels of exposure, exposure timing, and mode of action. To better understand this complexity, two papers. A recent systematic review highlighted the adverse outcome pathway (AOP) framework, which Dr. Bahadori noted was developed at EPA, as the best framework to estimate the potential impact of such exposures. Data emerging from NCCT in collaboration with Tox21 Program can populate the AOPs and facilitate a better understanding of exposure and health outcome relationships.

Noting the CSS StRAP, Dr. Bahadori articulated that the vision of the CSS program is that CSS will lead development of innovative science to support safe, sustainable use of chemicals and materials required to promote ecological wellbeing, including human and environmental health, as well as to protect vulnerable species and populations. She emphasized that lifecycle and life-stage considerations of exposure are critical in CSS. Dr. Bahadori also noted that CSS will focus

on assessing mixtures rather than individual molecules. The centerpiece of CSS will entail embracing the uncertainty, complexity, and multifactorial systems inherent to environmental health issues.

The next topic Dr. Bahadori discussed was the activities of CSS. She noted that CSS endeavors to populate the chemical effects data landscape and build knowledge infrastructure by generating health effects data and making them publicly available. CSS will also develop publicly available tools to facilitate the rapid, efficient, and effective evaluation of chemicals. The program will promote a complex systems understanding by investigating emerging properties and complex chemical-biological systems and probing how disturbances affect the system over time. Finally, CSS is committed to actively translating and delivering their data, tools, and knowledge.

Dr. Bahadori gave an overview of how CSS operates. She highlighted EPA's research labs and centers as the locations where the science is conducted. She explained that EPA also collaborates closely with other federal partners, on topics such as nanomaterials, since the data needs are great and the issues transcend the Agency. Dr. Bahadori also noted that EPA engages with a broad array of community stakeholders, including environmental health advocacy groups, animal rights groups, industry, small businesses, and many others. Finally, she pointed out the CSS team members.

Dr. Bahadori introduced the CSS 2016–2019 StRAP, which articulates new research ambitions for the next four years. Feedback from the SAB and the BOSC was instrumental in shaping the StRAP. To make the program translatable, CSS will build tangible case studies within each one of the topic areas that relate to a significant issue that is relevant to each of the program and regional offices. Based on the success of the first StRAP, CSS is in the position to better inform risk assessment. The new StRAP will focus on quantifying cumulative risk using the AOP framework, shifting toward predictive modeling and away from evaluating apical endpoints, continuing to emphasize the lifecycle perspective, protecting vulnerable and susceptible populations, and exploring higher throughput approaches.

Dr. Bahadori spoke to the design of the CSS program next. She explained that CSS is an extremely dynamic and interactive program, with three research projects (Chemical Evaluation, Lifecycle Analytics, and Complex Systems Science) and one translation topic (Solutions-based Translation and Knowledge Delivery). She noted several research highlights from each of the project and topic areas. Dr. Bahadori also covered the program's budget by topic area. Complex systems science will receive 36% of the funding for CSS in FY2016. Lifecycle analytics, chemical evaluation, and translation and delivery will receive 30%, 21%, and 13%, respectively.

Dr. Bahadori also covered the FY2016 key products by topic area. The Chemical Evaluation project will focus on delivering additional high throughput data for the AUR-TPO assay, validating medium and high throughput developmental neurotoxicity assays, and developing new analytical and computational methods for non-targeted chemical screening. Under the Complex Systems Science project, the key product will be a network of well-developed formal AOP descriptions related to molecular initiating events (MIEs) of high importance to the Endocrine Disruptor Screening Program (EDSP), including estrogen receptor agonism and antagonism, androgen receptor agonism and antagonism, thyroid axis disruption, and disruption of steroid biosynthesis. Dr. Bahadori noted several key products planned for the Lifecycle Analytics

project, including updates to the Distributed Structure-Searchable Toxicity (DSSTox) Database and developing a methodology for rapid lifecycle inventory generation, among others. In terms of key products for the Translation and Delivery topic, she explained that endocrine in vitro data and computational data will be compared to existing EDSP Tier-1 guideline methods to inform prioritization within EDSP.

Dr. Bahadori discussed the efforts to integrate across the six Agency research programs. She pointed out the integration of the existing and new epidemiology data with the data generated through EDSP, AOPs, and virtual tissue programs within the context of children's environmental health as an example of successful cross-program integration. She noted that roadmaps, similar to the one that facilitated the integration surrounding children's environmental health, exist for other areas such as environmental justice, climate change, as well as nitrogen and co-pollutants and gave several project-level examples.

Dr. Bahadori asked the subcommittee for questions and comments.

Dr. Leszczynski asked whether EPA is coordinating with other agencies internationally to address the 80,000 chemicals that Dr. Bahadori mentioned. Dr. Bahadori commented that trans-national collaboration is a hallmark of CSS's work. CSS collaborates with the European Commission as well as the Japanese Ministries of the Environment and Health, Labor and Welfare. She noted that much of these interactions is mediated by the Organization for Economic Cooperation and Development (OECD), but collaborations also takes place nation-to-nation. CSS works closely with the European Union (EU) on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and EDSP. CSS also works closely with Japan on pharmaceutical and water issues. Ultimately, the Agency's authority to implement the science drives the extent of such interactions.

Dr. Somasundaran commented that although information might be shared internationally, weighting factors will likely differ between countries based on specific economic and natural resource factors. He asked whether an index to compare weighting factors across countries exists. Dr. Bahadori replied that she is aware of efforts to develop sustainability indices, but while CSS can contribute data to the development of such indices, it cannot focus development itself.

Dr. Klaper stated she does not see how the research and collaboration with other entities and stakeholders connects to the regulatory function of the Agency. Dr. Bahadori replied that the regulatory influence occurs through work performed by the program and regional offices that is informed by CSS research. Examples were discussed in detail under separate charge questions.

Dr. Solomon asked which CSS program conducts the research on complex mixtures. Dr. Bahadori responded that she was resistant to putting "complex mixtures," specifically, in the StRAP, as many entities endeavor to make progress on assessing complex mixtures, but do not. She explained that CSS incorporated complex mixtures into the case studies.

Dr. Vorhees asked how CSS evaluates the differential quality of available data and how that is communicated to end users. Dr. Bahadori replied that existing data are sparse, and CSS does not have the luxury to qualitatively assess data, although they are subject to quality controls. All available data are used.

Dr. Somasundaran asked how data generated based on different test systems are used and extrapolated. Dr. Bahadori explained that OCSPP dictates which toxicity tests are accepted for each rule. CSS contributes data, but the acceptability of these tests are negotiated. CSS also contributes data to the debates surrounding how data are extrapolated across species and how relevant current test systems are.

Dr. Waters inquired about the extent to which CSS is able to use data generated by the Children's Environmental Health Centers to drive the focus on developmental endpoints for which CSS hopes to develop assays and models. Dr. Bahadori responded that data generated by hypothesis-based research have been harder to integrate into CSS's toxicology framework, but the molecular epidemiology studies are quite useful. Conversations regarding how to use and integrate data are ongoing. Dr. Waters followed by asking, given the National Academy of Sciences study on chronic low-dose exposures, how CSS integrates that information with its focus on developmental endpoints. Dr. Bahadori answered that if low-dose effects relevant to health impacts are demonstrated, the traditional toxicity testing paradigm will need to be reevaluated. This will provide an opportunity to bridge the data gap using CSS's newly developed assays.

Dr. Somasundaran asked how decades-delayed health effects are tested. Dr. Bahadori discussed the importance of complex systems science and the exposome to help understand the influence of early life exposures on later-life health outcomes.

Praising the ambitions of the new StRAP, Dr. Stevens wondered whether CSS is resourced well enough to deliver their key products within the FY2016–2019 timeframe, given the intricate interdependence of the various research programs. Dr. Bahadori acknowledged the ambitions are extreme, but countered that they are necessary. The enthusiasm for computational data will diminish quickly if the potential uses are not demonstrated. The StRAP indicates that CSS will begin to shift the research trend away from apical endpoints approach.

Given the long term ambitions of the StRAP, Dr. Johnson recommended including key "proof of concept" questions that CSS can answer throughout the FY 2016–2019 timeframe as a way to measure the program's progress and success. Dr. Bahadori responded that it is her hope that the case studies will achieve a similar end.

HHRA Program Purpose and Design (General Charge Question 1)
EPA Overview given by Dr. John Vandenberg

Dr. Vandenberg, the National Program Director of HHRA, discussed HHRA framework and how the program is structured in order to provide context for the charge question discussions. HHRA addresses all Agency mandates, including the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Food Quality Protection Act (FQPA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resources Conservation and Recovery Act (RCRA), and TSCA, to provide broad support to strategic goals related to children's environmental health, environmental justice, climate change, nitrogen and co-pollutants, and cumulative risk.

Dr. Vandenberg continued to explain that the research programs within ORD, such as HHRA, provide the scientific foundation for regulatory decision-making and implementation of

regulatory activities that support the Agency's overall mission. HHRA often operates between the research and risk management communities, interpreting the science to identify exposure-response information that supports Agency decision-making as well as communicating critical data gaps identified by risk managers back to the researchers.

Dr. Vandenberg explained that HHRA supports Agency risk assessment by providing both risk assessment tools and the exposure-response assessments themselves. HHRA develops the methods used in the risk assessment process and establishes provisional peer-reviewed toxicity values (PPRTVs) in work products such IRIS, Integrated Science Assessments (ISAs), and community and site-specific risk assessments. He also noted that the program is designed to allow for stakeholders involvement across several phases, such as scoping and problem formulation, as well as during the evaluation and outreach/training phases.

Next, Dr. Vandenberg highlighted the HHRA FY 2016–2019 research objectives, which include:

- Efficiently supporting a range of decision making with an agile, fit-for-purpose portfolio of robust and responsive assessment products that characterize risk and potential impacts to human health and the environment.
- Refining risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods, and technologies.
- Enhancing data access and management systems to support transparency and efficiency; provide outreach and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.

To meet its research objectives, Dr. Vandenberg explained HHRA will focus on the following nine projects:

- IRIS Assessments
- IRIS Updates
- ISAs and Scientific/Regulatory Support
- PPRTV Assessments
- Site-specific and Superfund Regulatory Support
- Cumulative Risk Assessment Methods and Applications
- Advancing Hazard Characterization and Dose-Response Methods
- Applying Emerging Science to Inform Risk Screening and Assessment
- Risk Assessment Support and Training

Dr. Vandenberg also gave an overview of specific tasks that fall under several of the projects. In the context of Site-specific and Superfund Regulatory Support, HHRA will provide quarterly reports to the Superfund Technical Support Center (STSC) and the Ecological Risk Assessment Support Center (ERASC), as well as technical and review support for Superfund and other Agency priorities.

For the Cumulative Risk Assessment Methods and Applications project, Dr. Vandenberg noted that HHRA will develop approaches for cross-species data integration, incorporate multiple stressors, apply genetic and epigenetic data to inform susceptibility, and apportion multimedia exposure and risk across human and ecological receptors.

The Advancing Hazard Characterization and Dose-Response Methods project will focus on advancing methods for systematic review and evidence integration, advancing quantitative methods, advancing methods for benefits and uncertainty analysis, characterizing determinants of risk, and conducting workshops on major risk assessment methodology issues.

The four tasks under the Applying Emerging Science to Inform Risk Screening and Assessment project are disease-based integration of new data types, characterization and quantitative application of high-throughput screening and other data-mining derivations, Dosimetry21: advancing multi-scale dosimetry models to incorporate AOP/Mode of Action (MOA) and biomarker data, and the evaluation and application of new exposure data and methods.

Finally, Dr. Vandenberg discussed the Risk Assessment Support and Training project, which includes tasks to develop and maintain essential software and support tools and to develop and apply risk assessment trainings.

Dr. Vandenberg ended his presentation by asking for any comments or questions.

Dr. Klaper asked how HHRA assesses its program needs and how are these incorporated into the long-term program strategy. Dr. Vandenberg answered that HHRA acts on short-term research goals and activities, but also recognizes that some topics are complex and require more time. Program partners recognize the value of these endeavors, which allows HHRA to envision longer-term goals and focus on short-term and long-term research goals simultaneously.

Dr. Somasundaran asked whether HHRA is advancing quantitative methods that will be able to assess trace exposures, such as those on the order of parts per trillion (ppt). Dr. Vandenberg replied that, for trace exposures, the dose-response relationship is extrapolated from animal toxicity studies that are conducted on the order of parts per million (ppm). He continued that the key to determining which model is most appropriate is based on MOA. If a MOA might occur at low levels, the dose-response relationship will be linear even at low levels.

Dr. Beamer inquired how HHRA addresses one chemical potentially causing multiple outcomes. Dr. Vandenberg answered that HHRA typically focuses on one chemical at a time, but looks at the multitude of associated health outcomes.

With the remaining time, Dr. McPartland commented that AOPs seem to play a central role in translating CSS research and asked Dr. Bahadori how CSS balances the biological complexity of dynamic systems science and AOPs that are more static. Dr. Bahadori replied that AOPs are not static. They are a way to think about alternative testing strategies. The biology does not stop at a linear understanding of an AOP. CSS evaluates the complex interactions of the different pathways, which feeds into the development of the next suite of assays required to perform the chemical evaluations.

BOSC Discussion of CSS Posters
CSS and HHRA Project Leads

Dr. Solomon began by reminding the subcommittee that this section of the agenda was for a brief sharing about what the subcommittee had seen and what grabbed their interest during the poster session. She noted everyone was able to disperse and see different posters.

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Dr. Somasundaran stated he was overall impressed with what was happening with the projects. One comment he made regarding two posters he saw was he had always thought what was needed when given a structure of a chemical was a place where that structure could be plugged into a computer and a result could be predicted. A good example of the structure-property relationship is how it is possible to modify the properties just by changing the structure slightly, which would be extremely complex, but should be an aim. He mentioned one of the posters he saw that approaches that almost having a library of chemicals, one should be able to predict what happens.

Dr. Johnson explained what stood out to him was the critical nature of looking at metabolites. If they look at a list of Tox21 chemicals, they don't address the metabolites that occur in vivo. This is a critical issue. He mentioned that it can be done confrontationally by going through and actually predicting all the metabolites of any compound, but to actually get some kind of data that relates to those metabolites is critical because some of those chemicals will be metabolized, virtually 80–100% in the body. It's not the original compound that is there. He thought that was an area that should be looked at in more detail. The second thing Dr. Johnson mentioned, which was very specific, was the tipping point characterization coming from a high-content screening of various chemicals using Cyprotex as the supplier of the system. Having done this previously himself, that particular assay was set up at 1, 24, and 72 hours. He noted that was not the way to do the appropriate high content screening. It is to do a continuous 72-hour high-content screening and the software is already there to do that. Every chemical is going to be slightly different. That is a better way to do it without costing any more.

Dr. Beamer said she was amazed by the breath, depth, and complexity of the problems CSS is faced with and stated the program is doing amazing work. She acknowledged the concern of it being overly ambitious, and she wished they could get CSS a higher budget because the work is so important. She also mentioned the importance of partnering with their external institutions because there is a lot of potential for synergy. Dr. Somasundaran asked Dr. Beamer by external institutions, if she meant within EPA. Dr. Beamer said EPA, outside, and globally given its relevance to daily life. Dr. Beamer noted she doesn't think the public knows the work they are doing and how it affects daily life and finding ways they could integrate might be a way to obtain more resources. Dr. Somasundaran suggested Dr. Beamer write a paragraph describing her suggestion.

Dr. Stevens explained he received a good answer to his tipping point question that he had asked earlier. Tipping point is described as transitioning from an adaptive to a non-adaptive state. The question it raised was when low-dose chronic exposure is discussed, was adaptive okay? In an environmental exposure situation, if the biological system is actively adapting to the exposure, he asked was that not adverse or is any response considered adverse? He understood the idea of the state transition. Dr. Stevens stated that they thought about it much the same way and had a really interesting conversation about the data CSS had collected from different methodologies that matched nicely with some of the data they had, particularly the collapse of oxidative stress being a tipping point from adaptive to progressive. He still thought there was a need to take that term, if it is going to be the point in which you declare something "significant," and define what a tipping point is. Is it adaptive to progressive or is it something prior to adaptive and adaptive itself? Dr. Somasundaran asked if it had to be a tipping point or if it could be gradual. Dr.

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Stevens replied by saying there are a lot of technical issues. What he saw was there was no dose-response relationship at the maximum response at the early time points. If someone then looked at the residual response at a 24-hour time point, there were dose response relationships underneath the maximum response. What was being seen is an increase in activity and then a return to an adaptive state. When the adaptive state began to collide with the maximum response rate, things begin to happen. So, if a measurement was taken at 6 hours, there wouldn't appear to be a dose-response relationship. At 24 hours, that relationship would be seen. Dr. Stevens explained he dealt with no observed adverse effect levels (NOAELs) in the pharmaceutical industry all the time. What is a NOAEL in an environmental exposure situation? Is there any biological response to arsenic enough to which that is not wanted (NOAEL), or is a no-effect level needed? That makes the tipping point any response at all versus an adverse effect level. He noted the definition required conversation. In application, it would require more definition.

Dr. Stevens also brought forth the concept of what evaluation and validation was for an AOP and what that meant. Where he arrived, and he was happy to be corrected, it appeared to be a very judgment-based process. He stated he had a long discussion about metrics and statistical models, how an AOP is converted to a statistical model, but it still came across at the poster as a very judgement-based approach. If it is, then it raised the question as to who's judgement and what the validation of a judgement-based process was versus a curve analysis to determine adequate performance in separating false positive and false negatives. Dr. Stevens was impressed with the quality of work as well as the staff at the posters. Those were two elements he thought the subcommittee could consider regarding the effectiveness of the overall programs.

Dr. Solomon stated she was also quite impressed with the posters, and she was only able to scratch the surface. She immediately came across a poster on thyroperoxidase (the new assay being developed) and the amazing process on developing new assays for the thyroid pathway. She was struck that the CSS program had been criticized for not adequately capturing thyroid effects. That poster showed responsiveness to those concerns and that there have been resources put into looking at the entire thyroid pathway and identifying important places of that pathway to put assays, and then developing assays because where none existed. She mentioned a story of the possible development of a new assay looking at thyroid hormone transport mechanisms. She believed that was encouraging. Dr. Solomon thought there was also a theme appearing on the topic of validation that Dr. Stevens mentioned, although it is not validation. She noted two posters—one looking at consumer product mixtures and one examining surface water mixtures—looking at trying to predict toxicity based on component chemicals in those mixtures. The surface water poster also tested the mixture itself to compare (even though she mentioned this was still not validation, per say), but to get an idea of how predictions were working. She thought those were promising and showed interesting and good thinking. Dr. Solomon noted testing the mixture might need to be done more on the consumer product side. She stated she noticed very good work and then mentioned the topic concerning AOPs. She explained there was a wiki she thought was very creative, but when she asked about it, it didn't seem like there was a lot of participation yet from the broader academic and research community. There seemed to be efforts to address that, but it seemed like if there were a way to get that started it would be great, but it wasn't there yet. She was trying to think about if there was any advice they could give on that issue. She concluded by saying there were many great posters.

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Dr. Klaper mentioned two things caught her attention. She did have some experience interacting with people in EPA from her fellowship in the past, and after seeing the posters, there seemed to be much more interaction among different groups. The fact that there so many groups are interacting and coming together is very exciting. From an ecologist standpoint, the fact that the research is going from the molecular to the ecosystem, or at least to the population and community-level questions, is also very exciting and encouraging. What she and other subcommittee members were grappling with was trying to make that connection, especially with the big emphasis on the ToxCast program. Dr. Klaper mentioned she knew it was generating tons of data, but figuring out what to do with the data was still in question. She had seen that it is still not providing what they need to model from one end to the other. While holding promise, she didn't see how it was going to go end to end. One of the reasons was from the quantitative aspect of it falling into how much gene expression or protein level needs to change to end up with outcome at the end. So while CSS might be trying to get away from the apical endpoint, and trying to work backwards, and while it may be easier to connect molecular data to something also molecular, she mentioned there still needed to be some kind of indication that is important and how much of that change ends up being important. She didn't believe they are there yet, not by a fault of EPA, but if that is what they will "hang their hat on," there was still a ways to go. There might be something to ratchet down the expectation on that and that it will be a quantitative final endpoint.

Dr. Vorhees stated the breath of work going on was incredible. As primarily an exposure person, she enjoyed seeing the exposure dosimetry poster and the promising and expressing screening. She had seen the quote about the 10,000–30,000 chemicals many times, so to see someone tackling that was a wonderful thing. She noted how on some posters and in the earlier presentations, there were case studies demonstrating the utility of the work and how it would be used and how effective it would be. Her question was how some of those case studies were chosen and how their success would be evaluated. She recognized that was an early stage and it may be hard to say what a measure of success was, but it was important to be explicit about that, even if it were to say "it is hard to say what the measures of success would be right now." Dr. Vorhees mentioned they should work toward that and those were new methods and confidence must be built. She believed it would be helpful for real measures of success to be part of the process. She explained there was some of that in the StRAP, in a section called "Measures of Success," but it was more of "this is a project we are going to finish" rather than "this is how we are going to evaluate this project is being implemented the way we hoped" and whether it is being used or has promise to be used.

Dr. Leszczynski commented he was very impressed with how a group of people from different backgrounds were able to work together to produce data. He had one general concern; he knew EPA needed to provide data for thousands of chemicals, but if they were developing computational methods, they needed to be careful because some of those methods aren't exactly accurate and there are many different conditions that needed to be included. The data might not be accurate when it is obtained using very simple programs. One poster he mentioned was on cerium dioxide in diesel fuel, and he found it very interesting. He continued by saying there was not money to continue this project, but hopefully EPA will obtain more money to help these projects. Dr. Somasundaran followed up on the cerium dioxide topic by explaining it is said to be toxic. On the other hand, he said he was aware of work that says it is not only not toxic but it can

even mitigate toxicity, and the mechanisms are not understood. He mentioned that there was a gap there in knowing why some of those things are observed.

Dr. Waters followed up on the AOP development project Dr. Stevens was discussing. What occurred to her in looking at the development of putative AOPs was that they are relying on a lot of data that are kind of static—one condition, one concentration, or one time point. That doesn't allow one to computationally infer either direction or dependency within a pathway. That's where judgement comes in by pulling out that information and actually making it an AOP. Combining that piece of information with the tipping point poster, which she found very interesting, raised the concept that in order to calculate the tipping point, both dose and time data are needed. She suggested they think about that in the future during development and validation of some of the assays for the AOPs. They need to collect that information at least for case study chemicals so that they can computationally be able to make those predictions. Dr. Waters also added she was impressed to see the poster on the incorporation of exposure because seeing how incorporation of that information changed the rankings and the regulation of the chemicals is not surprising but was great to see. She noted it would help with the engagement of the other offices and eventually for incorporation in risk assessment, which would be crucial. Dr. Somasundaran suggested she write that information down.

Dr. McPartland stated she was impressed with the putative AOP poster as well, specifically the point of the discovery approach to developing AOPs versus assuming a specific AOP *a priori*. She asked how work that is being done (i.e., AOP wiki and having experts building those AOPs) will be integrated with the more discovery type approaches to developing AOPs. Dr. Somasundaran asked Dr. Bahadori to clarify.

In response to the questions, Dr. Bahadori began by saying she would give the members a roadmap of responses. On the subject of computational chemistry work some members brought forth, she mentioned one of the key products for FY 2016 was in fact the development of databases of computational characteristics. She stated Mr. Todd Martin was leading the effort, along with a team within NCCT, to begin to develop tools for computational predictions from structure. It is not an easy thing to do, but it is a big axis of new activity that would begin. If it was not made clear in the StRAP, she wanted to clarify it at the meeting. That is a very big area of work for CSS. Dr. Somasundaran commented that with the hundreds of thousands of chemicals, that kind of approach would be useful. Dr. Bahadori said it is useful because ultimately, they had started tackling those 80,000 chemicals and at most, they had only completed 2,000–3,000. Their goal was to pull in an arsenal of tools, including the computational chemistry tool, and to use read across and use quantitative structure-activity modeling to begin to be more predictive, instead of having to test everything. She commented they had made significant investments in that area the past year.

Dr. Bahadori responded to Dr. Johnson that it was interesting he brought up metabolism, and they have acknowledged that as an issue. She stated they don't know whether incorporating metabolism necessarily would have changed the outcome of their studies, but they know that would be an open question. From the environment and ecological side, they would have a very large group at the Genius Bar the next day and attendees would get to see a demonstration of the Chemical Transformation System (CTS) being used in the environmental area to predict the biotransformation and its products. On the human health side, they have done some of the

TOXCON work, but what they were just able to do was obtain some resources from their innovation group, that is allowed for very specific ideas that manages some innovative approaches, to develop a challenge for the community out there to respond to them and help them know there is a way to physically incorporate metabolism into their battery of assays. That is a new challenge that just got resourced.

Dr. Bahadori addressed the AOP wiki questions next. She first suggested members address their questions to Dr. Stephen Edwards and Dr. Hines from NHEERL at the Genius Bar the next day. They would be able to explain the efforts they have done. She then explained they do not want people to superficially access the AOP wiki and "slap" an AOP out there; they want people to make resourceful commitments that they will actually follow through and commit to certain levels of quantitation in addition to discovery.

In response to Dr. Klaper's questions in regard to the broader applications of ToxCast, Dr. Bahadori suggested she speak with Dr. Carly LaLone and Dr. Edwards at the Genius Bar. The assays are the assays, they don't represent a full biology and that is understood, but the experiments are being designed to connect the dots.

Dr. Bahadori responded to Dr. Vorhees on the measures of success next. She mentioned Daniel Hicks was there to help figure that out. She said he is a scientist of a different perspective who focuses on the measures of effectiveness and success. On the other AOP discussions, Dr. Bahadori mentioned it would be helpful to go back and look at the blending of discovery and development application. She told the members they would hear from Dr. Vandenberg and Dr. Jarabek and what they were grappling with is that they are enthusiastic and supportive, but how to do it is still a big question. She was hopeful most of that would be answered the following day.

Subcommittee Discussion of CSS Scope and Implementation of Research (General Charge Questions 2 and 3 and CSS-specific Charge Question 4)

Chemical Evaluation, Lifecycle Analytics, and Complex Systems, CSS

To address the next charge question, Dr. Bahadori announced that she would give specific examples of work CSS has completed. She commented that the charge question addresses the development of case studies and the ways they engaged strategic partners in this effort. Dr. Bahadori added that she combined charge questions 2 through 4 for the purpose of discussion, as all three explore the effectiveness of the program, and would focus on the core research topics rather than research translation, which the group discussed later.

When CSS began developing the strategic research action plan, CSS program activities were scattered and there was not much opportunity for integration. Resources were also not sufficient. In 2013, the scientific team, laboratories' and centers' leadership, and Matrix Interfaces assessed their achievements based on the products of the first strategic planning activity. The group ranked the achievements, evaluated the progress of that science to determine what was possible technologically, and developed a proposed plan for integration. This was an addendum to the existing strategy. The program and regional offices gave feedback and the new StRAP was presented at the following Connectome meeting in May 2014. It became clear that the science was getting tighter, but it was still extremely difficult to demonstrate who was going to use the generated data.

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Dr. Bahadori elaborated that in 2014, CSS utilized focus group meetings to identify program office and regional office needs as well as meetings on specific scientific topics to identify knowledge gaps and understand why, despite such high-quality research, the program was not making headway. CSS went back to the focus groups and requested help generating case studies that would either help the program offices and regions or help CSS identify what more to do. CSS presented a number of case studies at Connectome 2015. Dr. Bahadori pointed out a few examples, including a case study on cumulative risk of chemicals with similar modes of action (MOA) and another on conducting a cumulative risk assessment using high-throughput data in addition to exposure and traditional toxicology data across a given pathway. She reminded the group that these case studies required a large amount of time and effort and the program offices and regions completed the majority of the work.

Dr. Bahadori also discussed several examples of targeted meetings. The first example was the Endocrine Disruption Screening Program (EDSP) thyroid integration meeting, which responded to the need to understand the role of thyroid hormone in the disruption of the endocrine system to the degree that estrogen and androgen are understood. She recounted that a thyroid hormone subject matter expert was recruited to work across EPA's laboratories and centers to develop what is now known as the thyroid research program. Resources and scientists were redirected successfully. This shows that if a priority is clearly articulated, engagement and programmatic changes can be effective.

Next, Dr. Bahadori discussed the concern over the release of nanoparticles, specifically silver, into wastewater streams and the inability of waste water treatment plants to address this type of contamination. She noted that at the time there was no understanding of the scope of the issue, so the nanomaterials meeting focused on recent research on nanomaterial releases. The conclusion of the meeting was that levels of nanoparticle releases are significant, but the health effects are similar to bulk silver. New research released recently by the National Institute of Environmental Health Sciences (NIEHS) indicated that nano-silver behaves differently than bulk silver when released into the environment. In response, CSS is conducting a case study to evaluate these data and incorporate them into the group's work. Dr. Bahadori reiterated that CSS is not ready to walk away from its work on silver. Dr. Bahadori concluded by asking the group for any comments or questions.

Dr. Solomon inquired about the additional markets for thyroid hormone data that Dr. Bahadori referenced during her presentation. Dr. Bahadori responded that she was alluding to the RapidTox project, which was a CSS project that was planned for the future, but the Office of Chemical Safety and Pollution Prevention has asked CSS to accelerate this work. CSS is developing a case study to respond to the desire to transition to effect-based, multi-pollutant monitoring from a chemical-by-chemical standard. Resources are being reallocated to accelerate these efforts.

Dr. Solomon suggested that Dr. Bahadori give a high-level overview of the RapidTox program, as some attendees may not be familiar with it. Dr. Bahadori explained that the purpose of RapidTox is to address the issue of performing lower-tiered risk assessment for chemicals that have absolutely no available data. The project is a marriage of computational work flow exercises that will demonstrate in modules how data can be drawn from different sources for the specific fit-for-purpose context. The workflow will transparently draw upon data from different

places and marry them to develop a putative point of departure value that can be used in a lower-tiered risk assessment.

Dr. Somasundaran asked about what it would take to predict the effects of nanoparticles with different traits, since the data on shape and size are sparse. Dr. Bahadori referred Dr. Somasundaran to Dr. Jason Lambert and his poster.

Dr. Beamer asked whether there is information on the effectiveness of the approaches to involve EPA partners or how many staff members these approaches reached. Dr. Bahadori replied that the scientific team, which is the core, has become much more connected, but there remains much room for improvement at the community level. Dr. Beamer followed by asking how the community-level partners might become more engaged. Dr. Bahadori responded that she is open to strategies to engage community-level partners, as CSS is just beginning to engage them. She also pointed out that they are interested in CSS science, but it is unclear how they can use it due to legal barriers, although they are willing to listen.

Dr. McPartland inquired how CSS plans to share the findings from the case studies within EPA or with a wider audience. Dr. Bahadori explained that sharing the data is the easy part, noting that the challenge is translating the data and helping the partners use it.

Dr. Stevens asked how CSS views its mission if it has external customers qualified to do risk assessment and can give them values they know how to use, but can also give them AOPs and other new things they can learn to use. He inquired whether the mission is split and how CSS divides between short-term wins and long-term changes in practices. Dr. Bahadori responded that CSS splits the effort, but not evenly. CSS is not a group of risk assessment experts. Through collaboration with HHRA, these points of departure (PODs) will be useful to some segment of that community. CSS needs to listen to determine what type of data these partners will use. Community-level partners note that while the focus on the EDSP is noble, it is inadequate because developmental neurotoxicology is a big gap. CSS is developing a suite of media assays and improving their performance, but the group's primary focus is addressing the paucity of data. Dr. Stevens followed by commenting that CSS is passing the burden to the risk assessors and asking where the roadblocks are in the process. He noted that CSS indicates there is a paucity of data, but the risk assessors cannot handle the amount of data they currently have. Dr. Bahadori answered that within the Agency, there are a lot of decisions that are made that are risk-informed, but not truly based on risk assessment. Program and regional partners told CSS that the risk assessment framework is not a tool they are using in certain decision processes. She commented that because CSS heard from the absence of data is still their partners' biggest barrier, CSS has continued its efforts to address that issue. Dr. Stevens inquired what BOSC can do to highlight this capacity restraint. Dr. Bahadori commented that charge question 4 specifically addresses whether CSS is working with partners to identify areas in which there are opportunities for fit-for-purpose knowledge delivery. RapidTox is a specific example of this. Dr. Stevens replied that he saw it as a charge question 2 or charge question 3 issue, but he believes the group should place it under a very specific question. He also noted that it struck him as being about the mechanism for incorporating information into risk assessment more than an evaluation of the scientific effectiveness. He closed by asking where he might put that in as a comment. Dr. Bahadori suggested that there is a place for such over-arching comments in the report.

Dr. Beamer asked Dr. Bahadori whether there has been a formal program evaluation performed to determine how CSS interacts with its partners. Dr. Bahadori replied there has not, since CSS does not have expertise in doing those types of evaluations.

Dr. McPartland followed by noting that there is potentially an opportunity for CSS to dictate the relationship with its clients by surveying their needs and determining where it can confidently provide risk assessment-related services. Dr. Bahadori responded that the fit-for-purpose is CSS's self-assembled approach for demonstration evaluation, which is steeped in consensus building. She underscored that risk assessment is not the primary concern, although she understands the risk assessment roadblock is coming. It is necessary to get the science and its application right first.

Dr. Somasundaran pointed out that titanium dioxide nanoparticles are reportedly toxic, but coated with zinc oxide to mitigate its toxicity. But it may still be problematic due to potential toxicity of dissolved zinc. There is a gap in the data here and the plan to assess it. Dr. Bahadori noted that the purpose of lifecycle assessment work is to consider the impacts of alternative decisions. She also highlighted another shift in the paradigm of the program, which is that many of the toxicity testing strategies focus on virgin chemicals that have completely different properties than when they are in biological systems, either human or the environment. With nanomaterials, the effects cannot be predicted accurately based on virgin chemicals outside of their biological system.

Subcommittee Discussion of CSS Fit-For-Purpose Translation and Knowledge Delivery (CSS-specific Charge Question 5)
Translation and Delivery, CSS

Dr. Bahadori began the discussion of charge question 5 by noting the importance of science translation and knowledge delivery. Every project in CSS has a translation component in it through the case studies or stand-alone webinars to communicate with program and regional partners and across ORD to other scientists about the direction of the project, new findings, or new interactions with OECD. She also noted another outreach effort that allows CSS to showcase its work among its three main audiences: program and regional offices, the stakeholder community, and the general public.

Dr. Bahadori also discussed the focus within CSS on increasing awareness of CSS research and its use in chemical risk decision-making in addition to voluntary efforts and other actions. CSS is focusing on screening and prioritization, estimation, modeling, and putative effects in order to push the boundaries of visualizing different uses of data within a risk-informed decision making process, as opposed to a strictly risk-assessment informed decision process. She also highlighted the importance of being meaningfully involved in the development of research and tools, pointing out that it is easy to slip into parochial approaches.

Dr. Bahadori focused on the use of webinars to increase engagement with CSS within EPA. She noted the focus on "bite-size science" webinar presentations that allow scientists to select which topics they would like more detailed information on in follow-up webinars. She commented that CSS also utilizes webinars to facilitate communication and collaboration between CSS, program

offices, and regional offices by providing project updates as well as enabling delivery of feedback.

Dr. Bahadori spoke about the CSS intranet, which she described as a one-stop shop for important CSS information, including research projects, project teams, project updates, CSS partnerships, StRAP and charters, news releases, and research products.

Dr. Bahadori reviewed the collaboration between CSS and OCSPP on EDSP as an example of how successful CSS has been in developing relevant science. CSS generated EDSP data, got feedback on the dose ranges, re-ran the samples, and made the data available for public consumption. She noted that the policy side of the Agency published in a peer-reviewed journal how they intend to use the generated data to prioritize EDSP Tier-1 testing and that it can serve as an alternative to current Tier-1 testing methods. Dr. Bahadori pointed out that both the turn-around time and seeking peer-review publication were both unprecedented.

Dr. Bahadori closed by underscoring the importance of engaging stakeholders and increasing their familiarity with CSS science. She noted that some in the community often criticize EPA risk assessments as not up to date, not consistent with science, and not adequately health protective. It will be critical for human health risk assessors and epidemiologists to understand, integrate, and use diverse sets of data to ensure the production of the highest quality and most impactful science.

Dr. Somasundaran commented on how impressed he was to learn of CSS's considerable effort to inform others of their scientific endeavors. He added that public opinion of EPA is not always positive, but increasing awareness surrounding important work, such as the work highlighted in Dr. Bahadori's presentation, may help.

Dr. Beamer asked for a definition of "fit-for-purpose." Dr. Bahadori responded that the first attribute of fit-for-purpose is to have a willing partner. Defining the condition under which CSS can design an experiment or collaboration requires a significant effort on the part of both CSS and its partner. For EDSP, fit-for-purpose meant that CSS could show that their suite of assays could help prioritize the chemicals requiring additional testing. That space has to be defined by the partner. Dr. Paloma followed by inquiring about the scope of fit-for-purpose. Dr. Bahadori explained that the scope can be small, but requests are sometimes large and are then broken down into multiple short-term arrangements.

Dr. Klaper asked whether the purpose of this type of science is to contribute to the regulatory process and what types of practices CSS utilizes to engage the collaborators in science that will contribute to the risk assessment process. Dr. Bahadori answered that CSS can work with the pre-design of chemicals. In fact, industry has started using these tools. But CSS would also like to be involved at the phase of pre-manufacturing, when a chemical is already being produced but has not yet entered the market. However, industry has not been interested so far. Dr. Klaper followed by asking how CSS will move forward in the pre-manufacturing level if there is no buy-in from the potential partners. Dr. Bahadori replied CSS knows what it can do, but its responsibility is clearly articulating the science questions that would benefit from the data. CSS must demonstrate that there is opportunity for transformative impact. She added that by speaking with those who are willing to listen and building relationships one partner at a time, CSS can take small steps toward an ambitious goal.

Dr. Somasundaran pointed out that perhaps a study could be conducted to illustrate how things would be if EPA did not exist or perhaps compare against corresponding efforts in other countries. Dr. Bahadori commented that she understands Dr. Somasundaran's point. The public understands the importance of preventing big disasters, but conveying the potential impact of low-dose, cumulative exposures is more difficult.

Dr. Vorhees inquired about the form that the two-way conversations between CSS and is partners take and will it include the partners reporting how they use the data. Dr. Bahadori responded that would be ideal, but for now it take the form of discussions about how the data might be used. She clarified that she meant two-way conversations as active listening to the partners, rather than telling them what they do.

Dr. Beamer suggested presenting the Genius Bar at additional conferences to increase familiarity with the available tools. Dr. Bahadori responded that doing so will require a divide-and-conquer strategy, as federal funds for engaging in scientific environments and meetings are limited. One priority is the annual meeting of the American Public Health Association.

Dr. Somasundaran suggested marketing the tools to high school students. Dr. Bahadori replied that she does high school outreach related to Science, Technology, Engineering, and Math (STEM), but she agreed that reaching somewhat unconventional audiences is critical.

Dr. Solomon commented that she interpreted the term "fit-for-purpose" in a broader manner than how Dr. Bahadori defined it. She pointed out that several National Research Council (NRC) reports, including *Science and Decisions: Advancing Risk Assessment* and *Toxicity Testing in the 21st Century: A Vision and a Strategy*, referred to the decision contexts and discuss fit-for-purpose in the risk assessment context. Dr. Bahadori clarified that she intended to further broaden the interpretation of "fit-for-purpose," which in the traditional interpretation means that something is fit for a specific decision-making context. She added that, to her, fit-for-purpose creates an opportunity to probe specific scientific contexts, as decision-making contexts have been narrowly defined by past activities. The regulatory context dictates the space for creativity, so fit-for-purpose can help widen the space for creative conversations.

Dr. Solomon also noted how diverse data types complicate the decision-making context, as risk assessors do not always have the necessary specific expertise. She asked whether CSS is working to integrate risk assessment tools for these types of situations. Dr. Bahadori discussed the CSS dashboard, which is not yet accessible, but will include toxicology and ecotoxicology data to begin to bring distinct data together in one place. She also described the need to integrate lifecycle assessment information, as well.

Dr. Stevens described his work to apply predictive tools in the pharmaceutical industry and discussed the notion of the sunk-cost bias tipping point. As he described in the context of EPA, the sunk-cost bias refers to companies that avoid developing chemicals that have a high probability of carrying a risk that EPA is interested in. As soon as the tipping point is crossed, the question then becomes about the certainty surrounding the occurrence of a given risk and companies default to developing the chemical until data exist to show a high probability of risk. He asked whether EPA observes this type of tipping point and how EPA might be able to address industries ability to enter the market at a point where there is no sunk cost of accepting EPA's

calculations of the probability of a given risk to occur. Dr. Bahadori submitted that EPA's standard of a "reasonable certainty of no harm" and its tolerance of the related uncertainty is different than that of the pharmaceutical industry. She noted that she understands his point, but does not believe EPA has reached the point of having a risk of sunk-cost bias and is, rather, at the point of accepting their position to make decision if the uncertainty can be described or quantified. Dr. Stevens clarified that he was referring to industry's sunk-cost, not EPA's. Dr. Bahadori replied, despite current uncertainties, some manufacturers are already using EPA's methods to determine which products should contain certain chemicals and to understand the lifecycle impacts. She did note that this information is anecdotal based on presentations at scientific meetings, as industry does not report these data to EPA.

Dr. Somasundaran wondered how and why the acceptance of EPA's publications on scientific topics may differ from those published by the American Medical Association or the National Academies of Science. Dr. Bahadori commented that the public or industry are much more accepting of publications on the applicability of certain technologies, such as nanomaterials, but less accepting of publications on their implications.

Dr. McPartland probed whether industry is using existing data in the context of new chemicals design or comparing alternatives to chemicals that have been through the ToxCast program. Dr. Bahadori responded that the focus is on the use of ToxCast program, but their science will also contribute to the development of new assays, as well. She also discussed a rapid exposure and dosimetry project, where EPA attempted to identify the chemicals used across classes of consumer products. EPA identified chemicals that were not known to be in certain products as well as chemicals that were not recognized. Dr. Bahadori noted she is hopeful than an EPA-industry partnership will help elucidate which chemicals are present in which products.

Dr. Johnson noted the information technology (IT)-intensiveness of these CSS projects. He inquired whether there is sufficient IT and whether that will be an issue for CSS moving forward. Dr. Bahadori replied that CSS receives the best available federal IT and is not poorly-resourced, but noted that the best available to the federal family is not necessarily the best available in general.

Subcommittee Wrap-up and Adjourn
Dr. Ponisseril Somasundaran and Dr. Gina Solomon

Dr. Solomon wrapped up the session by noting the amount of interesting information discussed relating to charge questions 2, 3, 4, and 5. She asked participating members to draft summaries of their comments as a means of responding to the charge questions and listed the members who posed questions or comments relevant to each question.

She closed the session by giving a brief overview of the next day's agenda.

Wednesday, October 7, 2015

CSS Genius Bar and Lab Tours, Room C-113
CSS Project Leads

DRAFT

Poster Session
CSS and HHRA Project Leads

BOSC Discussion: Poster Session, Genius Bars, and Lab Tours
Subcommittee

The subcommittee members reconvened after the poster session to discuss the Genius Bar, the lab tours, and the poster session. Dr. Somasundaran welcomed the attendees and initiated the discussion. Ms. Fleming asked the subcommittee to spend 10 to 15 minutes to discuss and reflect on the poster session as well as the Genius Bar and lab tours. Dr. Somasundaran stated he was truly impressed with the research occurring at EPA and believed that the public is not well informed of this research. He did state, however, that some of his questions raised the day before remained unanswered. Dr. Vorhees was overall very impressed and sensed that all the work is heading in a strong direction, but believed the writing provided beforehand did not reflect what she saw. Dr. McPartland commented on the integration of all the various research projects and wanted some time to think over the interrelatedness of all the information and over the transition occurring in HHRA. Dr. Beamer enjoyed the high level of research being performed and asked how that research could be implemented and brought to the community level, where it is most useful and impactful, and to bridge the disconnect.

Dr. Johnson extolled the high quality of science and enthusiasm of all the scientists he had witnessed during the conference, as well as the innovation, collaboration, and creativity, and wanted to keep in touch with the scientists. Dr. Waters was impressed with the integration across centers and believed the science was currently ready for immediate application in a regulatory context. Dr. Solomon was fascinated at the scope of work being performed, especially in regards to the zebrafish model outputs and the metabolites prediction tool. She agreed with Dr. McPartland in relation to there being a lot of different, overlapping tools, and it can be difficult and overwhelming to navigate them and understand their interrelatedness. She also advocated the subcommittee to go view a poster from the HHRA group comparing results from long-term and short-term in vivo model studies.

Dr. Weisel advocated for the integration of different research projects, especially in order to choose applications, and wanted ExpoCast and ToxCast integrated as a whole. Dr. Leszczynski wanted additions to the chemical transformation software exhibited and more sophisticated calculation methods incorporated. Dr. Stevens was captivated by the high level functionality of the tools developed, although they were lagging behind the pharmaceutical field to an extent in terms of complex system approaches because the research had not been worked on for as long. He asked what the subcommittee thought about the future of this research and these tools, and was particularly interested in the virtual tissue model.

Subcommittee Discussion of CSS Program EPA Response to Subcommittee Questions
Dr. Tina Bahadori

The subcommittee began general discussion of the CSS program subcommittee questions. Dr. Stevens discussed the AOP focus, which appears to be a mixture between knowledge based hypothesis generation models and statistical models. Knowledge-based hypothesis generation knowledge bases are judgement based and rapidly look for applicable hypotheses, while

statistical models are quantitative and look at hypotheses with statistics. He was uncertain how to make this transition between the two forms and was also unsure how AOP would fare as a risk assessment tool. One of the challenges is figuring out if AOP would need evidence from both statistical and knowledge based models, and the necessary emphasis and clarity on those two domains. Dr. McPartland asked how the statistical model approach was structured and if the model looked like a network based structure. Dr. Stevens responded that the virtue tissue model they had been examining was a computational model built on parameter input, mathematics, algorithms, and statistics. AOPs are ways of organizing the known into interpretable segments. There is a movement from linear progressions of initiating an event to a more statistic based model where you deal with populations. They need to be thought about and applied in fundamentally different ways.

Dr. Waters suggested statistical and inference based quantitative information is the kind of data that they need to move towards and they need to learn the sequence of events and outcomes happening in an AOP. The difficult part of the new process is not being able to capture the data necessary to build the models. There needs to be a concerted effort to collect the data needed to build those models. Dr. Stevens asked if there would be some definition in the future whether the AOP wiki was going to be knowledge based or more related to statistical risk assessment. Dr. Somasundaran chimed in there were good foundations for modeling, but for these models to be useful, they need to be appropriately related to the real systems, which is currently not examined by the models. To relate to real systems, they need to incorporate change over time and the transformation of mechanisms. A form of overlap, not total duplication, is necessary. Dr. Stevens discussed the complex systems modeling being a completely separate effort from AOP. Dr. McPartland believed it was important to communicate AOP is a traditional process construct to a different future vision, so people can become committed to AOP and move away from apical endpoints. Dr. Somasundaran felt they should not hesitate to discuss the gaps found.

Dr. Johnson discussed that the AOP is strongly based on the weight of evidence. New technology comes in and old technology evaporates. Some of this technology and new information is statistical and some is not. New modeling techniques all have uncertainty, and when they are combined it expands those uncertainties. The real question is how to change what the weight of evidence is, how it is explained to other people, and how it impacts new and old technologies. AOP is set up in the correct way, but needs to be interpreted in the correct way over time. Dr. Solomon discussed the discomfort with the use of the term “adverse outcomes pathway,” as it seemed reductionist. In the AOP wiki, there are two major issues. The first is the directness versus indirectness of the link. The second is the strength or weight of the evidence of the link. These issues can be confusing, as there can be cases where the link seems indirect based on dotted lines but then also appears to have a weaker association, even when that was not necessarily the case. Dr. Klaper recommended providing framework on how to interpret some of these dotted linkages, in order to understand how the interaction fits within the larger community. EPA is the one Agency that is responsible for environmental organisms. The zebrafish-human model used in the lab was a fantastic job of making the best of what was provided. The majority of what is seen is the human model information, with little data on the lab end to support the predictions and models. For example, there is a receptor that resembles the zebrafish receptor, but that is the extent of the connection. Furthermore, the tools have been linked to the program offices but not the regional offices. Dr. Klaper mentioned that the group

discusses susceptible organisms, but does not discuss which streams would be more susceptible, and does not include the regional offices, or the "boots on the ground." Dr. Johnson was extremely interested in the neurological lab and the primate models chosen for that standpoint. Primate tissues are available from the Cessation of Regulated Operations (CROs), as long as there is a collaboration with the CROs. Some animals are used and others are not, and it becomes a very nice model and very easy study group to retrieve. The collaboration and the study materials can be set up for free. There are variety of approaches to do so.

The subcommittee switched focus to a discussion led by Dr. Bahadori. She discussed that EPA had written a complete StRAP, but it does not reflect the breadth of everything as it is a very high level four year strategy. The writing of specific tasks is currently being developed and feedback from the current meeting will help inform some of those activities. There are a lot of future opportunities and it should be discussed how they are going to accommodate them in the next 6 months. She stated the NPD team would now have to work on interdisciplinary integration, now that the revision was out. There is a lot of cross project interaction, but graduate students tend to be introverts, and they must create the required relationships in order to integrate the work. The Matrix Interface from one lab to another needs to be crossed and advocated across projects. She hoped to see future progress in that direction the next time the group meets. The program is not focused on classical ecology work, and instead the central focus is chemicals. The project is controlled by a slowly evolving, regulatory testing strategy. There are new representative models and, until the program expands on the regulatory side, it has to match a replicator. Furthermore, most of the work is pesticide driven. There is a complex mixture of laws that drive what is possible to do on the regulatory side. There is not an opportunity to see what the AOP project looks like as a whole. The leaders of that project would need to demonstrate it, as it is one of the most complex projects. They do a lot of field work and have some of the best pathologists, and there was not a way to show all of that work during the meeting. CSS supports a regulatory framework and the scope of research needs to fit in that framework. The virtual tissue model (VTM) works on the topics that can support that regulatory framework. The VTM really informs the experimental design. The complex system applications are still very young because integrative teams are needed to study them. It is not a transition, it is a bridge. CSS will not invest in full elucidation of any one AOP or marry the concept. The AOP is used to organize what is known to predict what is not known. The tool is designed to inform risk assessment. The wiki helped create a space where everyone can contribute to the evolution of this assessment and take away from the AOP what they need to meet their own mission. It is a place to evolve shared concepts and resources but that does not necessarily meet the same objectives for everyone. This bridge concept allows the connection of molecular and system events and the informing of pathways. It is more of a network than a pathway but the name cannot be changed. However, in the project plan it can be better described as a systems approach rather than as a pathways approach.

Dr. Somasundaran discussed the eagerness of the scientists to use these models, but he understood that they would not be available until all the approvals eventually occur. Dr. Bahadori countered that the real issue was the Agency website was criticized as being inaccessible to the public. They created a beautiful and new website for the public, but it was not designed to support the complex technology they are trying to make publicly available. They are currently trying to resolve this issue. The classic issue has arisen, in which one tool cannot do

everything. The system can house the tool, but it does not have interactive capability, and it is then more of a static system than a dashboard. CSS is currently trying to find a compromise to this problem.

Dr. Johnson asked about the time frame of distributing the tool. Dr. Bahadori estimated it should hopefully only be a few months. They are working on a solution as fast as possible. The developer of the tool has had a manuscript ready for a year and a half, but she cannot publish it because the tool is not currently accessible. The impact is incredibly significant. They burden is on everyone that the manuscript will not be published if the tool is not publicly available. There is a limit to what the technology is capable of doing.

Dr. Somasundaran questioned if all the proper approvals for the technology were in place. Dr. Bahadori remarked that it had been approved on every level required, but the real issue was the public accessibility of the tool, which affects everyone. They have started to begin to take the tools to the regions, as there is usually a lot more innovation in the regions than in Washington. Dr. Klaper responded to the exciting potential of the tools, and asked if they could already be inserted in the research in the regions. Dr. Bahadori remarked that there will be a meeting in November to talk about AOPs, but the group currently does not have travel approval yet so they have not invited anyone yet. She asked for their recommendations to be articulated in the report over this issue.

Dr. Klaper mentioned that the Office of Pesticide Programs (OPP) is not the only program with regulatory authority for studying ecologically relevant organisms, and brought up regulations such as the Clean Water Act and Superfund. To not include the organism-centered part means the tool is not as strong, and the biology information needs to come along with the data development already available. Dr. Bahadori responded that CSS was included in the agenda, for the first time, on an aquatic life criteria meeting by OW in order discuss the tools available for the community. When the community saw the tools they gladly welcomed them and there will be another workshop hosted next year focused on the ways the tools can help the information and data to be collected. Dr. Klaper agreed with this involvement. Dr. Bahadori mentioned in this meeting, the pesticides and water programs were not really interacting with each other. However, including them on the same modeling team created an opportunity for conversation and to come up with solutions to the situation.

Dr. Somasundaran asked about mechanisms for one agency to interact with another agency when there is a gap such as this one. Dr. Bahadori replied most of the work is mechanism based, as the majority of their work is toxicology, which is also mechanism based. They work closely with NIEHS on Tox21 issues. With the National Science Foundation (NSF), they work on mostly chemistry and nanotechnology materials, not biology, but their next collaboration with them is biology-centered. Dr. Somasundaran asked, in the case of nanotechnology, if CSS had interagency interaction around the topic. Dr. Bahadori responded there was form of interaction around toxicity and there is one around exposure. Creating initiative is one thing and creating resources is another thing. When resources are available, relationships come about very quickly. Dr. Johnson mentioned they have listened to some of the roadblocks of distributing information from a public standpoint, and asked what the major recommendation would be to aid this process. Dr. Bahadori brought up the recommendation that describes what is seen as a barrier around IT issues and infrastructure. CSS uses a lot of contract support to integrate these tools,

which is a complicated process as the tools do not lend themselves to integration by law. CSS intervenes in this area with new projects and contracts, but this is also one of the most significant risks to the program.

Dr. Johnson asked if any other EPA member in the room would also like to answer that question. Dr. Vandenberg chimed in over the topic of the trends over time, as staff and resources have shrunk over time and the organization has lost critical capabilities. This is across the government, and not just the organization, but EPA in particular is heavily pressured. Dr. Somasundaran asked about collaboration with academics. Dr. Bahadori replied that CSS is in the universe of environmental science and associated with the collection of big data. The majority of the people in the room are in the government service (GS) category. Any of their organizations are given small authority to go out and recruit expertise to come in for very specific transformative needs, as expressed in Title 42. It must be a GS position if the job is associate with the core work or infrastructure of the Agency. GS positions are not quite as challenged over the use of authority in the matter. In short, CSS has authority over the matter, but is not always allowed to exercise it.

Dr. Thomas mentioned that IT infrastructure is really managed at the Agency level. The Office of Environmental Information manages infrastructure for the entire Agency, including ORD. IT infrastructure is managed at an Agency-wide level, and is not centered on customer service or specific needs of research organizations. The individuals hired to manage the IT infrastructure are paid on the GS scale, and they tend to migrate to private organizations which pay more than governmental agencies for IT work. Furthermore, there is a lack of accountability on whether or not government agencies meet IT expectations and goal marks. There are certain IT benchmarks that the organization does not live up to, such as the number of service calls or other metrics which are not adequately captured. Dr. Jarabek added that they also have issues over making data accessible or restricted depending on where they are in the process and IT infrastructure is an important factor for this issue.

Dr. Somasundaran closed discussion and stated it was time to break for lunch. In terms of reconvening, Dr. Vandenberg asked the members of the panel to join at the top of the steps in order to be taken to the showcase after lunch. There were two demonstrations in one conference room, and another held in a different room. He divided the members into groups.

HHRA Software Showcase, Building B Room B-249
HHRA Project Leads

HHRA Projects #5–9 (General Charge Questions 2 and 3 and HHRA-specific Charge Question 6)
Dr. John Vandenberg
- Site-specific Support and Emergency Response
- Cumulative Risk Assessment
- Advancing Hazard Characterization and Dose-response methods
- Applying Emerging Science
- Risk Assessment Support and Training

The chairs decided not to get subcommittee feedback on the HHRA Showcase at this time. Dr. Vandenberg started the session by introducing the HHRA members and shared several talking

points. He brought up charge questions 2, 3, and 6. HHRA is performing increasing amounts of outreach and communication, including partner meetings, monthly highlight and support bulletins, and public meetings and workshops. For example, HHRA has an annual program meeting to bring together program partners to understand their priorities. Furthermore, they have a great deal of involvement with the program and regional offices. They meet with the program offices routinely and work to engage partners in order to know their needs and the necessary timing. They try to push this information out through emails and news updates, although they also push a lot of information out passively through their website. HHRA holds a lot of public meetings and workshops, and they have IRIS public science meetings. The most recent one was on polychlorinated biphenyls (PCBs), and the one before that was on epigenetics. The next meeting coming up in December is about advancing systematic review. These topics cut across science issues. HHRA has a lot of assessment products and models, which are the resources that are used to support the scientific community as well as the modeling type of tools used to inform the risk assessments. The training aspect is also important as HHRA has been producing a number of modules, including a risk assessment training, which they provide to the program offices and regions as well as other organizations. There is risk assessment support to programs and regions, and a lot of tools and means used to provide that support, such as the Risk Assessment Training Experience (RATE) program. That has been very successful and positioned the Agency to be leaders in the field. HHRA has also looked at state travel, as it provides a way for them to share knowledge with a great amount of people. A major state-partnered program is the Interstate Technology and Regulatory Council. The next major step for HHRA is to bring scientists together at an international level. Currently, they have a lot of engagement with international organizations, like the World Health Organization (WHO).

Addressing Topic 3, community and site-specific risk, HHRA provides rapid response assessments and cumulative risk methods to address emergency response, Superfund site assessment, sustainability characterization, and community concerns. Project 5 addresses requests for regulatory support of site-specific and Superfund areas. This work is directly in response to a prioritized list of chemicals from OSWER from regional programs and other partners. The organization is called upon to help support short-term emergency situations, such as the spill in West Virginia. Dr. Vandenberg discussed the rapid response to support Communities Freedom Industries during the Charleston, West Virginia spill in greater depth, where HHRA was asked to develop a screening level. This rapid support demonstrates the group's response to previous BOSC recommendations and their increase in responsivity. Project 6 deals with the cumulative risk assessment program, and their methods and applications. It is a forward-looking effort to bring together what is known in order to summarize cumulative risk, using case study, cross-species, and epigenetic data, incorporating multiple stressors, and apportioning multimedia exposure and risk across human and ecological receptors. There has been an increased effort in looking at epigenetics, as there is a lot of opportunity to advance science in ways that are a little different by examining chemicals through the environment in which people live. The results of these studies can be used to support community health and safety. This effort is positioning the Agency to go from a chemical-centric view to an overall well-being view. They are looking at well-being as an important outcome, and it is not just human health they are considering as a composite of well-being. This type of work is highly complex, and case studies need to have definite bounds or they will never end. CRA is a well-

vetted platform to evolve place-based community assessment and to address environmental justice issues. EPA has a unique opportunity to advance CRA knowledge, including understanding stressor interactions, the incorporation of resiliency and well-being factors, and the integration of ecological assessments.

Dr. Vandenberg moved on to discuss charge question 6, over the research dimensions of the HHRA program and the proposed approaches for new data characterization and computational methods. He focused on Topic 4, the advancement of analyses and applications, which covers Projects 7–9. Topic 4 addresses the science challenges affecting hazard, exposure or dose-response analyses and the application of scientific, technical, and communication innovations to improve characterization of human and environmental impacts. Project 7 covers advancing hazard characterization and dose-response methods, Project 8 centers on applying emerging science to inform risk screening and assessment, and Project 9 addresses risk assessment support and training. The projects covered topics such as Health and Environmental Research Online (HERO) support of a systematic review approach and the combination of quantitative methods like benchmark dose (BMD) modeling with BMDS. There have been advancing methods for systematic review, which has been a challenge the last couple of years. Integration of topics such as epigenetics, toxicology, MOA, and exposure research, has occurred, in order to help risk managers have confidence in the conclusions. There are a number of chemical endpoints with difficulties, such as how to consider the combination of concentration, time and level of response and how to characterize and interpret different types of data. Overall, the conversation centered on connecting the dots between quantitative and qualitative data analysis.

SAB and BOSC had provided some comments on the capabilities and future directions of the CSS and HHRA research programs. They found them to be scientifically robust and well-aligned to the overarching EPA Strategic Plan, and emphasized their full confidence in the programs. HHRA is trying to build confidence through iteration and learning from failures and successes. They are looking at this flexible portfolio in order to use different approaches in a complimentary way. There were a few focus areas for advancing applications provided emerging technology will allow for the characterization of personal exposure environment. Risk assessment is not a monolith. It varies depending on the context of insights being drawn from the data, and how they will be used. HHRA wants to characterize application of emerging data and computational approaches across the risk assessment landscape, as well as integrate mechanistic knowledge into assessment products, such as high-throughput screening and AOPs. The work of scientists and researchers needs to be linked with risk assessors so chains of causality can be accurately and efficiently interpreted. The decision context for an assessment product should define the fit for purpose need and drive the application of data and approaches. There are a few major questions to cover when creating these new approaches: how can the data be connected together? Should it be qualitative or quantitative? Risk assessment is not a model. It is dependent on the setting being worked upon. The question is how this information can be organized in order to piece it together. One of the issues for risk assessors is the scientists collecting the data are throwing bits of information to the risk assessors, who are wondering where the missing pieces of the work and research are, as they are trying to make sense and use of this information. Information can be brought in and put together in a chain way to support different types of decisions.

Dr. Vandenberg then delved into Project 8 specifics, discussing the characterization of emerging science and methodologies, disease-based data integration, and multi-scale dosimetry to advance the application of AOP and MOA. For the disease based approach, there are a wide range of types of data that are related to that disease outcome and then can work backwards. This was what Project 8 was centered on. The other side of Project 8 was using dosimetry to advance application of AOP and MOA. HHRA is trying to recognize the issues as a risk assessor would and is facing difficulties understanding and making some of these connections. They are trying to get their heads around how to quantitatively summarize the issue. In terms of Project 7, he specifically explained the characterization of integrated determinants of risk, such as concentration, duration, and timing of exposure. Project 7 is related to the recognition that people are not all exposed to a consistent level of pollutants for their entire lives. These studies involve a type of exposure where the exposure level is very wide in respect to time. HHRA is trying to develop methodologies to use for the studies, and has to look at the case studies and recognize some limitations in the methods performed. A lot of chemicals examined are gases and reactive metals.

HHRA has had many crosscutting collaborations with CSS, Air, Climate, and Energy, Safe and Sustainable Water Resources, Sustainable and Healthy Communities, and the Homeland Security research programs, as risk assessment cuts across all EPA sectors. Collaborative effort between CSS and HHRA is demonstrated by the current efforts to use emerging science to inform the screening and prioritization of chemicals and the increase in regulatory values. The organizations are trying to recognize that risk assessors have difficulties making connections between exposures and outcomes, which is where AOP and MOA come in. They are not currently developing acute reference values, but hope to bridge the new information in order to look at exposure duration and responses.

In summary, HHRA is developing a portfolio of assessment products for improved public health, identifying issues and advancing approaches to arrive at solutions, and applying new technologies and data to refine analyses. Furthermore, HHRA supports communities with cumulative risk characterization of multiple stressors on human and ecological health, and educates and engages stakeholders to build capacity.

The floor was opened up for a question-and-answer period, and all members were invited to provide comments. Dr. Solomon pointed out that the group still needed to respond to the Showcase, and asked the members to include those reactions, too.

Subcommittee Discussion of HHRA Program and EPA Response to Subcommittee Questions
Dr. John Vandenberg and Subcommittee

Dr. Somasundaran brought up schools as an effective method of outreach and communication, and commented there were no schools listed. Furthermore, there was no measurement of community and combined effects, which is essential for analysis, especially when unusual outbreaks, such as Ebola, occur in communities. Dr. Waters asked if the HHRA Superfund technical support staff interacts with the National Institutes of Health (NIH) Superfund research investigators in order to bridge basic research and regulation. Dr. Vandenberg replied yes, the

interaction occurs, and the Superfund centers have their own number of technical experts as well. Ms. Annette Gatchett, the Director of the National Center for the Environmental Assessment (NCEA) Cincinnati Division, commented that she and Dr. Lynn Flowers have participated on calls with Superfund where they are asked about the research they are working on, and how they have provided provisional peer-reviewed toxicity values when there are no values. They have worked with them for some time and tried to leverage the resources. Dr. Waters asked if this is the case with Superfund investigators specifically, or if they had also worked with the regional partners. Ms. Gatchett replied they work with NIEHS and not directly with communities, which Dr. Waters remarked was a great opportunity available for them. Dr. Solomon asked Dr. Waters to clarify if she was suggesting connections with NIEHS funded Superfund centers or directly with communities, to which Dr. Waters responded she was referring to NIEHS funded Superfund centers. Dr. Flowers mentioned she performed that area of work, regularly providing feedback and interacting with the centers.

Dr. Vorhees brought up the earlier conversation about the cumulative risk assessment and how challenging it is, and specifically focused on the difficulties of dealing with non-chemical stressors. She asked if they could expand on these subjects, describe what they had in mind or specific case studies, and explain how much attention non-chemical stressors will receive as a lot of EPA's programs are chemical-centric. Dr. Vandenberg answered the area is highly dynamic and developing. There is a lot of Agency recognition towards certain mixtures like phthalates, PCBs, and other well-known mixtures. A recent challenge is that the Agency has been asked by the Clean Air Science Advisory Council to examine these factors, and found that there is a lack of research and studies on these combined factors of chemical and nonchemical stressors. It is even more complicated when analyzing community-stress levels. Regulatory programs are focused mainly on specific chemicals, but the Agency is trying to set the stage for combined mixtures by performing case studies. The organization is currently not there yet, but they try to look ahead before the programs are necessarily in place.

Dr. Weisel stated he had three major issues and comments to discuss. The first is that the Agency needs to recognize all sources of exposure in their analyses. The second is that they need to push sustainability as a priority, and wondered what was being done in order to encourage sustainability measures. Thirdly, the showcase seemed to focus less on research and more on how to interact with partners, stakeholders, and academics, which was nice to see as it shows how EPA is translating its work to others. Dr. Leszczynski explained the way research is being carried out is changing, as researchers are combining experimental and computational approaches. He then asked what the ratio of experimental to computational work would be for the next couple of years. Dr. Klaper asked about their interest in the integration of exposure data and how they were going to integrate that data. Dr. Johnson wanted a clearer definition of internal partners, and also wanted to know more about the workshops, especially how they were publicized, who was invited, and who attended. Dr. Solomon mentioned the topic of acute reference concentrations and risk assessments, as her region performs them and found them quite useful. She asked about their thoughts on including a subcommittee recommendation over this topic and also asked if the cumulative risk assessment issue is even possible within the parameters of a risk assessment framework. Ecological studies have worked better than human studies in that context. She loved the earlier tools demonstration and wanted the group to discuss more about the tools from ecological risk assessments. Dr. Somasundaran commented about the

different definitions of sustainability and emphasized the importance of defining the word whenever it is used, and asked for the panel to define the word.

Dr. Vandenberg started responding to questions and comments by covering the issue of internal partners. HHRA regulatory programs and regional offices are internal to EPA, and they have partners across ORD trying to address issues important to partners' regulatory activities, such as setting national standards and Superfund. Dr. Vandenberg used the term stakeholders to distinguish between the public and communities that are affected by those decisions. He makes the distinction that partners work with HHRA in order to make decisions and those decisions affect stakeholders. In terms of sustainability, there are a variety of ways to frame it. There has been a lot of argument over a general definition for sustainability. HHRA does not directly address sustainability, as it is not mentioned in the title. However, all ORD activities are targeted to address the broad definition of sustainability and HHRA centers on this broader and more general definition of sustainability. Regarding the question raised about acute versus chronic exposures, HHRA had started work on the issues, but out of Agency constraints restricted the studies as there were differing administration. Dr. Solomon asked if there was a possibility of decreasing those restrictions. Dr. Vandenberg replied in the affirmative, and asked the committee to make a recommendation in order to produce fruitful results. HHRA has been very resource constrained, and has often solely focused on chronic exposures because of that. They have recently been trying to deal with very short-term exposures that people are now capable of measuring, and HHRA is not entirely sure how to carry out the research. In response to Dr. Johnson's question, Dr. Vandenberg stated HHRA would be happy to include him on the list of recipients for the workshops and they would welcome measures on how to increase outreach for these meetings. Their website is trying to be ever more transparent and accessible, and they have recently pushed to enhance their webcast abilities in order to reach the broader community of people interested in the workshops as well as nongovernmental organizations (NGOs).

Dr. Vandenberg asked the room for further questions. Dr. Somasundaran asked how they determine rapid responses to problems. He asked, for example, for Ebola, if water treatment was the issue, and how soon they would get involved with an issue like this. Dr. Vandenberg replied their involvement with quick and emergency response situations is organized by the National Homeland Security Research Center (NHSRC). For the Ebola crisis, HHRA tapped into other parts of ORD. For the spill in West Virginia, ORD came directly to HHRA, as they looked at the issue and decided which parts of the organization to tap into, and HHRA responded to their request. The homeland security program is called Remedial Action Cost Engineering and Requirements (RACER), and HHRA responds immediately and quickly to address public health emergencies when asked by RACER. Dr. Somasundaran asked who specifically handled the Ebola case. Dr. Ramasamy answered the Office of Water, the Office of Ground Water and Drinking Water in particular, handles the waste water issues, such as Ebola.

Dr. Klaper commented on the tools, specifically the Expo-Box, which she felt was a laundry list of assessment tools. She mentioned it seemed like HHRA was just presenting a list of things they might consider confusing, and she was unsure how they evaluated which tool to use for what purpose. She asked them if there are ways of directing people to certain tools within that framework in order to help include other information in assessments, especially for people outside the Agency. Dr. Vandenberg explained there is a risk assessment portal, and what Dr.

Klaper is describing is a decision tool, which shows the users all the tools and databases available. Dr. Klaper pointed out HERO as an excellent tool to view EPA's decision-making process literature, and then asked about their response to integration of information about pulse doses versus longer term exposures. Dr. Vandenberg responded the current assessment work is targeted towards chronic exposures, but in this review HHRA wanted to examine whether or not developing tools that analyze the time and level or response is a worthwhile investment. The beginning of a program like this is underway, especially in program offices that have a need of short-term exposure analyses. The material provided to the subcommittee has project plans and descriptions listed with more detail on this subject.

Dr. Stevens commented, in the area of IT needs, there are computational IT needs, and then legacy IT needs, and the data HHRA has was not collected with IT in mind. Information collected needs to be properly organized and manually curated. He asked how BOSC could frame that problem and deal with the problem of legacy issues versus collecting new data. He wondered what they would need in terms of capacity to solve these problems, and what barriers they would have towards their work. Dr. Vandenberg responded HHRA is more closely related to a data user than a data generator, and the real challenge is having datasets that are accessible. The legacy data they work with is sometimes handwritten or in picture form. They are challenged to provide original data from studies, and need to look towards a future where there is interoperability and where they have access to the original data in a format and data system that is more easily available for analysis and manipulation. Dr. Bahadori commented on the need to digitize data and make it publicly available, saying CSS has been working to unearth and make available their legacy data. The Aggregated Computational Toxicology Resource (ACToR) database, for example, has harmonized the platform on which the data are collated and digitized, which is how they are getting around interoperability in terms of data streams. CSS data streams will need to be integrated within that specific context. Dr. Stevens questioned how they work with major journals around common data formats and asked the organizations to look into this subject. Dr. Somasundaran asked him to write up a section on this topic, and then informed the room it was time for a short break before moving on to the next section.

Program and Regional Office Perspectives on CSS and HHRA Programs (General Charge Questions 2 and 3)

Dr. Somasundaran brought the subcommittee back together to start the session.

Dr. David Dix, OCSPP

Dr. Dix, the Director of the Office of Science and Coordination and Policy in OCSPP, was connected to through the phone line, for the first presentation. He started by making some comments concerning the CSS research program and some of the significant tools and resources it has provided OCSPP, as well as some of the ways OCSPP are making use of them. He also highlighted the ongoing partnership they have with CSS and its researchers in terms of support, innovation, and ongoing translation of their research into regulatory practice. He discussed the recent OCSPP meetings with European chemical agencies, EU scientists, and a variety of other stakeholders, held to discuss progress made in endocrine disruptor screening process and the science of explaining chemicals in endocrine disruption. They are going to continue that discussion with OECD partners soon after. Furthermore, this week, other members of their office

participated in another OECD meeting over the validation of test methods group for ecological test methods. OSCPP has a very significant partnership OECD and ORD. In the past few months, they have seen a significant step forward in the application of new tools stemming from the computational toxicology and CSS program, such as high throughput screen assays and predictive models for biological pathways, which they have now validated for application in their endocrine disrupter screening program. These new tools are the first step towards modernizing the approaches for chemical safety and risk assessment for the OCSPP. They have begun this translation of the new science from CSS in their endocrine disrupter screening program and endocrine pathways. Future analyses will go beyond a reproductive and developmental focus of these pathways and eventually provide an alternative for much of the animal based toxicity approaches they are using for risk and chemical safety assessments. The new tools will allow high throughput analyses such as the extrapolation from in vitro to in vivo and exposure modeling. The higher throughout and predictive tools and models coming from the CSS program come together for a new future for chemical safety assessment. He applauded the progress CSS research has made that is readily translatable towards the needs of the OCSPP and lauded their setting the bar on the international level for the future of chemical safety assessment.

Dr. Jeff Morris, Office of Pollution Prevention and Toxics (OPPT)

Dr. Morris started his presentation by briefly covering the regulatory landscape that OPPT covers. They regulate industrial chemicals. There are currently thousands of unassessed chemicals in commerce without a whole lot of data on them, which is a major issue. There are about 1,000 new chemicals with premanufacture notifications every year which OPPT needs to make decisions on within 90 days, and there is currently no requirement that data be submitted to support those decisions. OPPT uses structural analogs to understand whether they may present a reasonable risk, but they work in a very data poor environment with weak regulatory framework for acquiring such data. This is where the CSS and HHRA research needs come in and how the organizations support their program. From CSS, generally speaking, they need information and tools to support single chemical evaluations. While they recognize the importance, both scientifically and environment health wise, at looking cumulatively at chemical evaluations, the OPPT statute generally requires they evaluate the risks of individual chemical substances, particularly for new chemicals. The high throughput and life cycle assessments are critically important for new chemicals. There is no real possibility OPPT is going to get through prioritizing and assessing the thousands of chemicals out there in commerce without using high-throughput approaches. For new chemicals, the extent CSS can bring these new approaches to enhance OPPT's current work on analogs and quantitative structure-activity relationships (QSARs) would be very useful. In the area of emerging substances, CSS is critically important. OPPT regulates nanoscale materials as well as biotechnology and genetically engineered substances. For those, in the new chemicals program, decision support tools, due the lack of structural analogs for these substances, are important and CSS is part of that program, as it is the projects going on there over nanomaterials that are very useful to OPPT. They have seen about 160 nanomaterial substances over the last several years, many covering base substances, and the CSS program is right on track developing those tools. In regards to HHRA, their work on risk assessment approaches, particularly approaches to help them integrate 21st century data in the weight of evidence for evaluations of existing chemicals, is very important work. The HHRA's IRIS program is also very useful to OPPT. There are a minority of cases where they need a

reference dose or concentration, because in most cases the exposure scenarios they are examining are less than lifetime. Nevertheless, the intermediate products used to develop IRIS products are very useful to OPPT. In fact, recent risk assessments have relied on those products of the IRIS process even though they did need the reference dose or concentration. IRIS is ensuring those intermediate products are recognized and are seen, in as of themselves, as important deliverables to the OPPT office. The office could not have done the work they have been able to without the IRIS products. The products have led to the IRIS values. Furthermore, Dr. Morris wanted to touch on the two charge questions. In both cases, both programs are good at involving OPPT and are responsive to their needs. The issues they do have are not with the programs but with ORD and the program offices, and the issue is the idea of science transfer. This challenge exists not because of fault of the ORD programs but due to the difficulty OPPT has in finding time to bring ORD researchers who are developing these products together with the OPPT scientists who are doing these assessments and chemical evaluations, in order for the researchers to know how to integrate these approaches into their work. They tend to underestimate the resource implications in doing so. It is a challenge for all to recognize and take into account the resource implications for technology and science transfer and factor that into operations. In summary, these two programs have already proven critical to OPPT's success and as they continue to spend more resources in the evaluation of existing chemicals, which they continue to ramp up, the approach CSS and HHRA are developing to advancing 21st century is critical to OPPT.

Dr. Kathleen Raffaele, OSWER

Dr. Raffaele, the Senior Science Advisor in OSWER, presented next. OSWER performs risk based decision making in three very different circumstances, which includes emergency response, clean up at contaminated sites, and national rules in their hazardous waste program. Different levels of information are needed for the different contexts, and in terms of fit for purpose, they have to decide what is appropriate to use. She gave a variety of scenarios and emphasizes the differences in amounts of information available for different scenarios, as well as the validation of that information. In some cases, they have no IRIS values or toxicity values for those chemicals, in which case they have to make assumptions without those values. They have to stand behind their data both in the scientific community and in court, so they want the most validated data they can find to back their decisions. They most often are challenged over their site decisions, and they need to have scientific evidence over the validity of their data. Dr. Raffaele talked about the questions OSWER was asked to address and how the organizations support their needs. OSWER has meetings frequently with HHRA and CSS and interact with them in a variety of ways. She rapidly listed interactions between the organizations. They currently are working with the CSS program to develop the RapidTox to meet their needs and have also participated in a lot of issues related to IRIS. They have quarterly Assistant Administrator-level meetings with ORD. There are many examples of where CSS tools support their program, and she emphasized the critical nature of ORD research in supporting the OSWER mission in a variety of manners. The IRIS values are critical to OSWER assessments. She emphasized the importance of the ORD technology support centers, which are key to OSWER regions and doing work in their sites. In respect to CSS, they are excited about RapidTox, which will hopefully lead to a better understanding of their data and program issues. They are looking to see how lifecycle and exposure modeling efforts might interact with our

program. As Dr. Morris said, they are looking forward to the collaboration between CSS and HHRA. They discussed with the organizations site-specific issues with respect to particular chemicals. They rely heavily on the *Exposure Factors Handbook*, which they use to do their risk assessments. They currently have very poor data for children, and are excited for future projects in this area. Some of the additional projects, such as benefits assessments for noncancerous endpoints, will be useful for their national rules work, as will cumulative risk assessment studies and developing additional methods for that. They are very interested in the study of acute and short-term values, which was discussed earlier. To get to the bottom line, HHRA core toxicity values and exposure factors are very valuable to OSWER in their ability to assess and remediate at sites. They are very supportive of this work continuing and future collaborations with both CSS and HHRA, especially in regards to future data and data streams.

Dr. Santhini Ramasamy, OW

Dr. Ramasamy, a Senior Toxicologist from the Office of Water, spoke next. OW has four individual offices including the Office of Science and Technology, Office of Ground Water and Drinking Water, Office of Wastewater Management, and Office of Wetlands, Oceans, and Watersheds. She was from the Office of Science and Technology, and their office provides science support to those different offices. With groundwater and drinking water, they provide help on the Safe Drinking Water Act, and for the other two offices they help establish criteria and provide a science approach. She provided a response to the two charge questions. HHRA has involved them in the strategic action plan, which has been overall very effective. They have had connector meetings with CSS, which were face to face and where StRAPs were provided, and OW was able to learn about new tools and communicate their input and priorities to the scientists in ORD. They have monthly implementation team meetings where they discuss the new tools coming out of CSS and where they provide their accomplishments. They recently put out health advisories for two cyanotoxins and released updated ambient water criteria for 94 contaminants. They looked at assessments from other partners, and they update the science. They greatly benefited from briefings with the office directors and Dr. Bahadori about CSS products, implementations, and workshops. They recently had a discussion about nanotechnology that was very useful. In terms of HHRA, they benefit greatly from their risk assessment meetings, workshops, and webinars, where they are able to communicate their input. They looked at the existing drinking water standards and updated them, and communicated their data needs with HHRA. OW wanted to stress that the organizations have to look at all of the peer reviewed information, which can be very difficult unless they are translated and interpreted in a way that is useful for policy making. They look to HHRA to inform them on decision and policy making. In terms of meeting their partner needs, CSS was successful in meeting with them during this planning and they also put out a policy paper on how new innovative tools could be used to do the monitoring and analytical measurements for thousands of compounds. They have to prioritize the drinking water contaminants, and RapidTox and HHRA helps with this process and the translation of all the complex information in order to support policy decisions. She ended by thanking both organizations for the opportunities they have provided.

Dr. Daniel Axelrad, Office of Policy

Dr. Axelrad, from the Office of Policy in the National Center for Environmental Economics (NCEE), presented next. NCEE's major role is supporting the media program offices in

conducting benefit cost analysis. That role influences a lot of the relationship their office has with ORD and the national programs in bringing together the economic and risk assessment science to inform the benefits and cost analysis. Dr. Axelrad started with HHRA, as he has had more activity with them. He shared a broader perspective on NCEE's work and how it relates to HHRA. Benefit cost analysis is required for all of the agencies major regulations by executive order. More and more over time, NCEE is hearing from the program offices that they would like their assistance and collaboration in helping them to quantify the human health benefits of their rules. They are finding that if they do not have sufficient quantified benefits incorporated in their regulations, those regulations have a hard time getting issued. There is an emphasis in improving NCEE capabilities in quantitative health benefits analysis. The key input from risk assessment in the health research side are quantitative estimates of risk at different exposure levels, which is what provides the tool so they can estimate changes in risk as exposures change in response to regulatory options. The traditional reference doses provided in risk assessments do not give the information that economists need to do that quantification in changes of risk for noncancerous outcomes. They have been focused on quantitative dose assessments. This work cannot happen without a cross-disciplinary collaboration between the risk assessment side and the Agency's economists. They have been working with HHRA for several years, and major milestone occurred in 2013 when they collaborated on an internal workshop with participants across ORD and media program offices on the needs for benefits analysis and non-cancer outcomes. The findings of that workshop laid the foundation for some of the elements in Project 7 of the HHRA Strap. The discussions were continued at both the 2014 and 2015 annual partner plan meetings. At the 2015 meeting, they had an important and constructive discussion about the needs they have in this area and what HHRA began to outline under Project 7 for supportive benefits analysis, uncertainty analysis, and dose-response assessment tools. That has been an important development for NCEE. The main concern for NCEE it that what is in the plan, particularly Project 7, is actually implemented. NCEE understands HHRA's challenge to support this work and getting assessments done by the program offices, especially as the program is resource constrained. He emphasized staff portioning off enough time to accomplish the key tasks of this program.

Regarding CSS, NCEE has had good opportunities to provide input to this program, through monthly partner series and AOP webinar series. NCEE views the work on AOPs as critical for the direction they are going in as it is highly important to draw connections between early biological changes and the ultimate apical outcomes. The assessments and assays may be going towards upstream earlier biological indicators, but ultimately the decision makers and the benefit and cost analysis are going to need that information on the apical outcomes. He emphasized high fully support to the AOP worked and thanked the subcommittee for the opportunity to give these comments.

Dr. Bryan Hubbell, Office of Air Quality Planning and Standards (OAQPS)

Dr. Bryan Hubbell, the Science Advisor for the Health and Environmental Impacts Division in OAQPS, within the Office of Air and Radiation (OAR), spoke next. His division is responsible for the review of the national ambient air quality standards as well as a variety of air toxicity and pollution assessments. They support national and international air policy and toxicity assessment. He was providing OAR's feedback on HHRA and their research program. They have benefited

greatly from the work on the development of IRIS and integrated assessments. The two OAR offices that most heavily work with HHRA are his office and the office of transportation and air quality. They are very interested in the new directions HHRA is taking, especially in addressing topics such as cumulative risk assessment, benefits assessment, and acute assessments. Regarding the charge question over the interaction with program offices, HHRA is very engaged with both OAR and OAQPS. They meet regularly with HHRA to discuss research progress, important milestones, and hot topic areas as they arise. The meetings allow OAR and HHRA to stay ahead on emerging issues and make sure HHRA activities have appropriate policy relevance. OAR engages with HHRA staff for other research opportunities as well as with outside organizations. Staff in both organizations have engaged in cross office details, which has built closer ties and has been an opportunity for OAR to understand and learn about HHRA and for them to learn about OAR. OAR wants to be involved and is currently involved in approaches to evidence integration for hazard identification. They want to see examples developed that include hazardous air pollutants with limited data, and which needs a benchmark, as it could have a serious regulatory impact. They have a number of chemicals for which they have a lot of data but they want to understand the implications of using these approaches where there is not as much data. In terms of risk assessment forums related to dose response method projects, cross office interactions between OAR and HHRA are very useful in making sure the overall perspectives on the issue are heard. OAR wants to continue be involved in the development of models of risk characterization. In terms of benefits and analysis methods, OAR is in the fortunate position to have an advanced program for benefits assessments. They have a great deal of information available for air pollutants, which have been through a great deal of peer review. Interested in the development of methodology in air pollution areas where there is a lack of data. From their experience, OAR has found it very important to include probabilistic responses and good characterization of values of outcomes as well as to bring in regulatory economists early in the development process to allow for more fit for purpose research. He gave one note of caution, in considering research directions and support of benefits analysis, HHRA should carefully consider which chemicals and health endpoints to evaluate given the resources available. Choices of endpoints should be informed by degree of population exposure, prevalence of health condition in the population, and the severity of the health outcomes. Choosing a low exposure or rare outcome could be very expensive with little to show for. Important to focus on the chemicals and health outcome that will have a big impact. In terms of cumulative risk assessment, OAR is involved with the Air, Climate, and Energy program in looking at multipollutant studies. They see the studies as a very big challenge, and EPA needs cross collaboration and some kind of roadmap so there is not waste of resources in developing approaches that do not complement each other. He also cautions on aggregate endpoints and not to miss the parts of cumulative risk that are important, especially associated with particular chemical or exposure pathways. OAR supports the case study approach and looks forward to working with NCEA. Lastly, he mentions their new portable FEM, federally certified sensors, the recent one created for ozone and having to deal with what to do with this high quality data across all the programs.

Mr. Robert Hillger, Region 1

Mr. Robert Hillger, the first of the EPA regional perspectives, thanked the subcommittee for allowing the regions the opportunity to speak. He brought up the fact that he was an engineer, but he had a lot of experience in the matter as he was the lead region representing 10 other

regions. He has been involved with ORD for a while, and has worked with four different regions across the country on a multitude of projects and research partnerships. He has worked with NPDs, and said that they understand when the connectivity between them is working and when it is not. There is a lot of research going on, and they are trying to find the nexus as to what is going well. There have been plenty of opportunities to go to meetings and see where it is not working. Everyone sees their priorities at the top of the list. With CSS, Dr. Bahadori has been their contact for 2–3 years and Region 3, the lead region, is primarily responsible for CSS, and they are trying to find their responsibility and priorities. They are trying to establish what makes sense for the CSS staff to be doing and then what should go back to the regions, which represent half the Agency. It is hard to reach out to all 10 different regions. He applauded Dr. Bahadori because she was persistent. The regions wondered how to go out to do this, and he would present an idea of where the connections are and what can be made. They brought Dr. Bahadori to Region 1, as they like face to face meetings. People in the regions are really busy, but as long as representatives meet with them in person, they are given the time. Regions need to be involved in order to express their needs and make a connection. They had Dr. Bahadori meet with their senior management as well as the research staff, as they are the individuals doing the work in the field. Dr. Bahadori was very patient and a great collaborator. They rotate the lead region position every two years, and they share and discuss a lot between regions. Region 3 decided they needed to do an internal survey after reading the StRAP, and asked their region staff and mangers to read the document and let the executive team know what they thought. They have talking points from all the discussions and meetings, which they will send an electronic copy of to the subcommittee. When they had those meetings, they found areas for opportunity as well as for improvement. After holding the survey and meetings, they added another group of people from OSCPP to help them work with green chemistry. The leader of that, Dr. Paul Anastas from ORD, took a group of people from the region as well as Dr. Bahadori and they worked on designing and adopting guidance for developing safer and healthier products. The Region also participated in the Connectome, which is a very great meeting for the regions to attend. There were about 4–5 people who would go down from each of the regions, and they were able to engage everyone. They set the table for working with CSS and learned some very salient points at the Connectome. The region felt it was important to bring the regions at the front end of things in terms of projects and research, as they are a sort of a client. They need to know what the regions need before they go to show them new ideas and projects.

Dr. Bruce Duncan, Region 10

Dr. Bruce Duncan, the Science Liaison for Region 10, was the next regional office representative to present. He joked his region had been hard at work putting up their science "dating profile" and connect with CSS and HHRA. In terms of the charge questions, the webinars are extremely valuable to them, especially once they are archived and are in collaboration with the regions. For the regional participation in the StRAP charter reviews, they have a whole champion's advocate type of approach they believe will be effective. In regards to CSS, the part of CSS that deals with partner driven research, which deals with short term high priority science needs and tailored solutions, the regions seek a little more clarity on how regions can access this opportunity and how the process works. Another program important to the regions is the regional research partnership program that allows the regional staff to train side by side ORD staff, and they appreciate the extent that CSS and HHRA support the program, as participants return back to

their regions with new tools as well as new ORD contacts. Dr. Raffaele covered the technology support centers and how great they are to the regions. OSWER and the regions are highly in sync on science needs and tend to speak pretty well with one voice to ORD across the regional and national program, which is a helpful model that seems to work for OSWER and the regions. The daily technological support does not get documented but it is of high value to the regions to have that access. They also appreciate how HHRA has been involving the regions in workshop planning. In regards to charge question 3, the Regional Applied Research Effort (RARE) program, which is a program by which ORD responds directly to high priority near term regional needs, improves the collaboration between the regions and ORD and has been very useful. ORD sets aside funding for these projects and the regions appreciate that contribution of time and resources. The RARE program is the best opportunity for regions to have their short and intermediate term needs addressed by ORD. It is a small level of funding, projects usually range from $50–200K and there are occasional problems with finding ORD staff. What the regions would like continued is the use of regions as incubators and pilot programs, which addresses both regional and ORD needs and missions as well as the national programs. Furthermore, they want continued work on the cumulative risk and integrative approach. Some of the issues they would like ORD to consider includes taking a look at the success of a program that is in the Safe and Healthy Communities, the Regional Sustainability and Environmental Science (RESES) Program, and try to emulate the components of that program that have been the most successful in CSS and HHRA. Another area to examine is strengthening ties with NIEHS and the Superfund program, as these ties could help with testing and applying CSS and HHRA tools that show potential for application to human health risk. Furthermore, for tools, it would be helpful for the regions to understand the lifecycle approach to these tools, such as how long ORD will support these tools and who will be taking care of the tools in the long run. Another area, which is more of a cultural change, is to make sure ORD endorses support of regional programs as a valuable component of promotion of staff. They are currently seeing a hit or miss approach and not yet a broad practice. In regards to the key areas of science harmony, the regions want to work better with both programs to match science issues and needs with past, current, and planned research. They should all work together as partners to look at compiled regional research list and help make the scientist to scientist connection. He thanked the subcommittee for their time and the opportunity to speak.

Mr. Bart Hoskins, Region 1

Mr. Bart Hoskins, an ecological risk assessor in Region 1, spoke. He is based in the regional laboratory, and so often has the opportunity to do lab and field work and support his ecological risk work. Many of the members of the region have been using CSS information, programs, and tools without knowing for a couple of years. In regards to charge question 2, Dr. Bahadori has come out to Region 1 to meet with the ecological risk assessors, which was helpful as they were given the opportunity to review the StRAP and circulated a survey to provide substantive comments on the topics that peaked regional interests. The Region was invited to Connectome, which was a great tool and showcase of a lot of CSS projects and products. In regards to charge question three, in terms of CSS, the ecological risk assessors communicate with monthly calls, for many years, with Mr. Michael Kravitz, who runs an ORD support center for ecological risk assessors where they can bring questions up that are vexing them and he helps them find ORD scientists that can help. There is usually a product or white paper that comes out of this process

that is then shared among all the ecological risk assessors across the regions. The regions have all been using ECOTOX and related programs for a long time, which are critical to their day to day operations, and are also essential for performing due diligence checks for long term chemicals and seeing if there is something new to pay attention to. There are three region related projects looking at metabolomics, patellagenin, and endocrine disruption related to personal care products and pharmaceuticals in rivers. There is one in his region, in Massachusetts, that is associated with the RARE program and has been very successful. It has been very interesting way to look at a lot of new tools coming out, especially since the river is heavily dominated by sewage treatment flow and is fairly impacted. In terms of recommendations going forward, the region found the StRAP confusing. In the regional survey, many researchers expressed they were not interested in products, but only because they did not know what they were. Many did express they were interested in AOPs, but they would have been more interested if the StRAP used terminology such as biomarkers and sublethal effects. The regions need help translating how bringing these new tools and products into their work could be cost effective and improve the work, as well as understanding how seemingly unrelated studies could actually show a population level impact. In regards to Region 1, they have a robust regional science council and Science to Achieve Results (STAR) grant days, which are very useful. Mr. Hoskins recommended combining ecological risk and ORD meetings with the Society of Toxicology meeting, as all major stakeholders will already be assembled there in one location. He also expressed, for Dr. Anastas, the appreciation of the interdisciplinary working group that includes all ten regions and major stakeholders that was established by ORD, meets once a week, and has been exceedingly successful.

Dr. Kristen Keteles, Region 8

Dr. Kristen Keteles, a Toxicologist with Region 8, presented. She liked that the subcommittee referred to the region and staff as the boots on the ground, as they are on the front line in terms of citizens and sites. They deal with a lot of issues in their communities, including exposure to chemicals in consumer products, serving as expert witnesses, and fielding calls from concerned citizens and stakeholders. She has been involved with CSS since 2010 and has seen the program evolve firsthand to meet the needs of the program offices and regions. She has had the privilege of seeing many of the tools they are already using come to fruition and she was very excited for using the tools on the horizon such as RapidTox and AOPs. Some tools they are currently using are for metabolomics and vitellogenin production. They have used these tools to see a difference in estrogenic activity below two different wastewater plants and have found they were very sensitive tools to compare wastewater treatment technology and they can be used in monitoring programs. She hoped the tools could one day be used for more regulatory applications. The major hurdle stopping that usage is linking the bioactivity response to actual adverse ecological impacts such as change in population. They believe AOPs hold the key to being able to make that linkage so they have great hope for that research. She reiterated that RapidTox shows a lot of promise. At Connectome last year, she presented data from an actual site where they only had toxicology values for 50% of the chemicals. ORD helped them assess risk, as it fell inside the appropriate risk range even though it was missing half of the necessary toxicology values. ORD responded to the situation with RapidTox, which will hopefully help with data poor chemicals. It will take some policy changes, but it is more efficient to go build the tools, see what the science can do, and then inform the policy. She has not been as involved in HHRA, but her colleague

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Wendy O'Brien has gone to the HHRA meetings and helped inform the research. The issue of episodic exposures was raised and HHRA responded with setting up a workshop to lay groundwork to develop some tools and methods to assess risks for short-term, episodic, repeated exposures. HHRA was invaluable with the Gold King mine release. The HHRA program reviewed the values of the screening results and ensured the integrity of those numbers so they could make a timely decision to reopen the river. There are some challenges to overcome, especially surpassing the regulatory hurdles in order to use the tools in a regulatory context. Furthermore, sometimes it is hard for regional scientists to make a connection with ORD staff at that level because most of those connections are ad hoc. The regional scientists do not really get to interact much with ORD scientists, especially with all the travel budget cuts, even within the own Agency. Even with brief meetings with ORD counterparts, they do not really know what the regional scientists are working on. There needs to be mutual understanding between the regional scientists and ORD on what work is going on and what tools are useful and would be useful. One of the ways to help augment this understanding is using an application called Skillport, which involves using a portion of time to connect with other scientists. Furthermore, ORD should use regional science liaisons more in order to increase connection. She does not lay the blame solely on ORD. She commented that regional scientists are very busy, potentially introverted, and possibly skeptical of some of these new tools, and may not be reaching out enough to make these connections. She wanted to encourage ORD not to give up, to keep pressing forward in the development of the tools, and eventually regional staff would come around. She thanked the subcommittee for the opportunity.

Dr. Ron Landy, Region 3

Dr. Ron Landy, the ORD regional science liaison for Region 3, was the last regional representative to present. He started by thanking the subcommittee for the opportunity. He provided extensive input in the notes they gave, but since the subcommittee heard so much about the regions from the other representatives, he decided to focus on other topics. He hoped they had recognized that it is really critical to involve the clients in the problem formulation early one or they would never be successful in responding to their partner's needs. When dealing with the regions, it is important to remember they are dealing with a lot of different cultures and each of these regional cultures have other places they are trying to serve, such as states, tribes, and communities, and that they are trying to deliver good products out to. ORD cannot just bring a product to the regions at the end of its production and then tell them to run with it. They need to keep the regions involved throughout the lifecycle of product development, translation of the research, and application of the research. This involvement leads to ultimate effective use of the product as well as regions reporting back about the product, which is what ORD really wants to hear. Both CSS and HHRA have made a strong effort in this area, especially about getting involved in the problem formulation. Dr. Landy has attend all the major collaboration meetings, including the Risky Business and Connectome meetings, either virtual or in person, and expressed that it was very difficult to get regional workers the ability to travel there. Therefore, ORD needs to put emphasis on virtual participation. Both programs are improving in this aspect. In addition to that, the programs need to keep the collaboration alive after these meetings, which they both have tried to do. For example, in regards to the temporal exposure issue, there was a lot of discussion at the Risky Business meeting, and now there is a collaborative planning effort for the workshop between ORD and five different regions. Getting the regional people involved

early and keeping them engaged is valuable, especially to get their management support. CSS had a great novel approach with webinars that included two minute flash presentations. The regional attendees often get overwhelmed with the sophistication of all these projects and they really liked the two minute flash presentations to identify the projects of interest. The RARE program is unique because the ideas and needs are regionally driven. Most of the work out of ORD is driven by ORD scientists. RARE, however, goes from regions to ORD. Partner driven research and champion's advocates are all efforts trying to get the regions involved in the lifecycle of a product and setting research development on a path that will meet their needs. The Regional Research Partnership Program (R2P2) regional partnership will now allow ORD people to go out to the region, which promotes the flow and exchange of information, and is also a training opportunity for ORD workers to go out into that regional culture and establish a new communication channel to deliver the research back to their lab. The CSS client meetings have been great and has provided an opportunity for regions to be involved, not just in RARE or in extramural research, but also in intramural research. Regions were able to provide comments and contributions to the writing of the Request for Application (RFA), which is looking at the ecosystem effects of chemicals, and the regions will hopefully be further involved in the lifecycle of the RFA. There are loads of ORD seminars to attend, which can be difficult, but ORD has been making special efforts to make these meetings a professional development opportunity. This combination has been very beneficial and has provided the ability to gain continuing education credits. Lastly, ORD has recognized and responded to the need for training in risk assessment, as the regions are receiving a lot of new risk assessors that do not know all they need to know about risk assessments.

The regions provided one more collective comment and thanked Dr. Bahadori for her work in really engaging all of the regions and taking the time to figure out what works and what does not work. She helped cement the fit between the regions and CSS. They also thanked Dr. Vandenberg and Dr. Jarabek for doing the same with the regions and HHRA.

Dr. Somasundaran thanked them all for the information they have provided and the time they have spent. He then opened the floor for questions and comments from the subcommittee about the presentations.

Subcommittee Questions and Discussion

Dr. Solomon thanked everyone for providing the subcommittee their input. She wanted to address a few key points and comments that jumped out at her, which the subcommittee could build off of and fill in the gaps. There were a lot of CSS directed comments about the tangible uses of the CSS data around evaluating new nanomaterials in the TSCA program, the creation of harmful algal bloom (HAB) fact sheets, evaluating data poor chemicals at Superfund or other cleanup sites, and the potential future use of the habitats contaminants list for data poor hazardous air pollutants (HAPs) and other uses under TSCA in the future. There were a lot of acknowledgements given to RapidTox as well as metabolomics and patellagenin assays and utility. In regards to HHRA, there was a lot of interest in shorter term values, especially as OPPT does not use reference doses (RFDs) and reference concentrations (RFCs). There was an almost universal call for short-term, acute, and episodic exposure values. There was a call for soil and dust ingestion data to be improved. There were two new and not before heard comments that she wanted further conversation and explanation. The first was for more unified dose-response case

studies, and the second was over cautions about aggregate risk assessment. There was an HHRA compliment for their work on the Gold King mine incident. There was also a lot of conversation about partnerships with Connectome, the Risky Business conferences, flash presentations, R2P2 training, the RARE program, as well as general informal responses. Dr. Solomon seconded the state perspective given on ORD communication and participation level, as her CalEPA branch has been requesting the CSS program for information and assistance on all kinds of things, and HHRA to a lesser degree and their region has been received with great patience and wonderful attitudes. She liked the idea of regions as incubators and ORD taking the time to understand the region needs before product development. Dr. Solomon also seconded Dr. Keteles points to strengthen the connection to Superfund research program centers. She asked for further description of Skillport, as she had never heard of it before. She gave kudos on the risk assessment trainings from HHRA. She ended her comments by saying there was a lot of feedback they could wrap in as they develop their responses for the next, and asked everyone add comments to any issues she missed but to try to hold questions until after commentary discussion.

Dr. Somasundaran commented there seemed to be some collaboration between some regions, and some between regions and ORD, while others are asking for a lot more collaboration and connections. He asked Dr. McPartland if she still had a question on this topic from earlier, and she replied that the question had been answered but she had some commentary. Dr. McPartland expressed how helpful it was to hear all the presentations, as they had influenced and change her perception about uptake. She noted the motivation and enthusiasm, which she noted was not the rate limiting factor, and the barriers were training, exposure, and the ability to connect with ORD and get involved with the tools. She asked how useful having more time for interaction directly with ORD would be. She believed extra interaction would accelerate thinking about how CSS tools could be used in regions and various offices. She asked how realistic it was to have more of these types of interactions and real hands on engagement. Dr. Bahadori responded it was just a money issue. The regions cannot travel for as much as they would need to in order to keep up with ORD. It is not enough to go to one region at a time. ORD needs to figure out topical cluster meetings, support the travel, or piggyback on another meeting. She herself has put aside $100,000 for resources for travel and resources for a meeting. However, she did not know that in the federal government, if the money has not been tagged as travel funds, it cannot be used as travel. She had to learn how to work within that system and define the ways to get travel support to come to meetings. Understanding the system, she now just has to find a creative way to do it. Mr. Hillger added how important these meetings and connections are. In regions, they must have defensible data, and the number one thing region scientists want is a procedure they can use to write a permit or whatever the project is that will be defensible. ORD researchers and staff can be essential in this process, and the face to face meetings are where these connections happen. It is important to from a community of practice, as researchers are always looking for someone who can find help solve the problem. He brought up Skillport. Mr. Hoskins added to the Skillport notion, talking about a clearinghouse where people can find the individuals who can help them on a project and can help to really dig in on the problem. He discussed work detail and being able to coming to these meetings, which is common in headquarters, but not is a rare opportunity in regions where they have to crank out work every day in order to get it done in the fiscal year and cannot just vanish for an extensive time period.

Dr. Klaper pointed out that it is more than just a money issue, but it is also a time issue, which is what the regions are indicating. Furthermore, it is a language issue. People can have the best intentions when they come together meet, but then can just be two people talking past each other. When talking about communication with regional offices, it is almost like an educational issue. As a scientist working with engineers, for the longest time she did not understand what information the engineers needed. It was not until started directly communicating and discussing the issues with them that she was able to relate and synthesize their inputs into her work. It is a total misconception of what exactly is needed. Additionally, it seems like a connection issue on the ORD side as well. This issue was brought up when discussing when OP researchers are trying to do their own modeling but they do not have the necessary data for the chemicals involved. The problem, how to make up for this lack of data, is different at the regional and federal level. There is a huge focus on molecular data and trying to go farther and farther back, which is understandable from a science and modeling perspective. However, when hearing from the regional offices, it is clear apical endpoints are still so important. It is important to look at the mechanistic point of view on chemistry, but the apical endpoint information is still concrete and very necessary, especially in the ecological world, and should not go away.

Dr. Beamer said she heard the desire for more science to science interaction and different expressions of this interaction. She asked how communication and working together can happen more and be more widely encouraged. She wanted ORD to work with the regions as a client and then stay connected through the translation, implementation and documentation process. She asked if there were monthly calls on new tools interested regional people could jump in on, so there was not a big of a knowledge gap when the tools came out as there is a big learning curve on these things. New tools are intimidating and it is very difficult to incorporate them into existing practices. Graduate students need to be trained in these news tools in order to become the next risk assessors. In summary, regions need to be incorporated throughout the process, even just through conference calls, and need to be integrated more throughout the lifecycle of the project.

Dr. Vorhees asked about sensor technologies and what their promise might be. She added some comments about a research group. Dr. Bahadori replied there were many sensor research areas supported through collaboration with the White House and citizen science, as well as the pathfinder innovation program. There are separate pockets of resources that are awarded to groups of collaboration among regions, programs, and organizations to tackle these new issues. There is one working group over pollinators coming up. The very first time they wanted to schedule a first project meeting for the working group, the legal people in the office wanted to know what the ethical implications were of the work and the plans for data, so right away the project was delayed. The first meeting for the group with the ethics officer is finally occurring next week. Dr. Vandenberg commented Region 5 was very involved in air sensor research, as have many of the regional liaisons and federal agencies. New types of sensor data are coming in, such as the 1 minute ozone detector as well as the portable detector mentioned earlier. ORD is trying to get all the regional and the other federal agencies connected on the issue and on the same page. Dr. Hubbell added that one of the challenges EPA is facing is that the research and discovery occurring on these air sensors is happening a great deal outside the Agency. EPA needs to keep up with it and lead from ahead, or they will be far behind. They need to encourage a broad conversation on how the sensor data in interpreted, generated, stored and delivered to

different audiences. Dr. Vandenberg remarked HHRA had the California air directors come out and discuss these issues of EPA with them. They have had a workshop every year about this topic, as air sensors are a rapidly dynamic yet exceedingly important area. Dr. Solomon said community groups were already using these new tools in California, and the South Coast Air Quality Management District was testing them in their lab and posting data on their website for interested community groups.

Dr. Weisel brought up plans for lifecycle tools and the comments on how long tools were going to be supported by ORD. He felt the issue was very important, not only for the long-term, but also for the short-term, where ORD has to support the constant change of the tools, and provide the necessary training and dissemination of information about the changes in tools so they are still accessible and useable by the scientific community. Dr. Bahadori mentioned the National Renewable Energy Laboratory (NREL) was launching a lifecycle center of excellence because of the impact it will have across the board on all work. She emphasized that when models and tools are developed from a research perspective, sometimes 80% certainty is enough, as full confidence can be too costly to maintain. The ECOTOX database was lost because it cost close to $1 million to maintain and to curate for use in decision making. She asked if they try to have full certainty for one tools, how many of these can they realistically do it for. One tactic they thought of was to shed a bunch of tools and make them public, but she said it seemed unacceptable. She asked the group for any advice they might have on creating sustainable tools.

Dr. Solomon noted the topic was very important and she flagged it for the discussion the next day. She added, related to the topic, that many of the tools are moving targets. The CSS dashboard constantly has bits of information changing. She asked how much faith they should put on the data they see at any one time. It is a tough issue, because researchers want the information out there and do not want to wait until the data is at 100% certainty, but it is also frustrating to see it shifting around and changing. Dr. Weisel added the comment that when those tools are evaluated, they are frozen in time and a pdf is provided explaining which results were used in the evaluation. There may be points where the data needs to be frozen so the static system can be maintained while the development system is being worked on. Dr. Bahadori mentioned here experience with California highlighted the notion that every little change can matter. They had to freeze the dashboard in time in order to do the versioning and make the changes. They ran into problems, as the areas under the curve had changed on the dashboard during the process, which resulted in a massive quality change, and they had to redo the process which set them back three weeks. CSS is learning by doing and learning how important the process and data release is for databases. People do not want ephemeral data, even though they want high quality data. Dr. Jarabek added a comment about versioning vs metadata management and keeping the database curated. She stated that if there was a change made to a version, then that is information that should accompany the data on the go forward when it happens. The whole issue come full circle back to all the IT problems, and the question of whether or not the programs have the type of data management that allows them to trap what occurs with the data.

Dr. Duncan thanked the subcommittee for starting to chew on the issue of the lifecycle of tools so the regions can understand ORD's thoughts on how this will progress, how regions might be partnering in that process, and if down the road there might be a transference of these tools to a community of users and how that might happen. In regards to accelerating the interactions, the

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Regional Science Liaisons are working hard to deliver regional priorities on science needs and issues to ORD and appropriate programs and those tend to be about 15–50 per region. That will give the regions a good database of around 300–400 types of needs to work on and common themes to examine. Furthermore, the regions are looking for a way to make staff to scientist interactions, both opportunities for face to face meetings but also for opportunities to put out needs and understand what ORD is working on as well as contact with the people necessary in the process. The regions are on a learning curve together with ORD in trying to find out how to work at different levels of prioritization and make these interactions happen.

Ms. Fleming stated that there were no public comments on the discussion, as required by FACA, and said they could continue discussion.

Dr. Landy posted a message on the webinar. There are a variety of vehicles on regional ORD engagements to improve interactions. More information could be provided if it would be helpful. ORD has made significant improvements in the last few years and continues to explore more options. There was just not enough time to discuss today.

Dr. Solomon had question for Dr. Raffaele and maybe Dr. Ramasamy on the issue of analytical chemistry. She said it was her experience at sites that they look for a whole list of analytes and a whole list of tentatively identified compounds (TICs), tentatively identifiable compounds, which might be present. They mention these somewhere in the lab report, but do not know what to do with them. Her area has been looking for ways to wrap that information back into the process. She assumed the same issue would happen in surface water sampling. She asked if there was a feedback loop pathway between offices and programs asking for information on this and compounds that may be popping up. Dr. Raffaele referred to compounds on their sites that they do not have information on and mentioned that sometimes they know what they are and sometimes they do not. It is a conundrum because people cannot analyze for substances when the toxicology value is not available, because it is meaningless without it. There is a vicious circle because the chemical cannot be searched for because there is no value, but also since there is not a value, it cannot be clear if it is there or not.

Dr. Solomon asked how they could get out of the Catch22 situation. Dr. Raffaele replied that if they could make some structure, gather the information to identify the issues and the structure, and could get sufficient confidence in the read across information, they could try to include those bi-structural analogies as part of the risk assessment. This might motivate some generation of data where the researcher could either include the results in the risk assessment or say there is not really a problem and it does not need to cause worry. There are a lot of potential paths to take. Dr. Solomon asked if they could develop a case study around that. Dr. Raffaele said they had talked a lot about the exact form this case study would take and if it would allow a better way to pull more information about chemicals for which they do not have values into the risk assessment project. Dr. Keteles agreed wholeheartedly with Dr. Raffaele. She said they are restricted to what they have methods for and that is what they focus on. The see a lot of TICs. If they do not have values, then they do not know if the chemicals are confirmed so they are often excluded. There is a lot of promise in computational toxicology. There is a Denver river where they shipped water samples on ice to run them through an estrogen screen as a mixture in order to look at the estrogenic activity. They would be happy to develop a case study for RapidTox once read across connections to CompTox are developed. Mr. Hillger agreed with the comment

that not enough was mentioned about the states. All ORD products that come out of the pipeline are of interest to the states as well as the regions, as they are doing the same kind of analyses and research as the regions. The states want to be involved in this process as well and invited to trainings and review. EPA is not, and has never been, good at marketing and business. They have the money to do the research, cleanup, and regulations, but no one is really marketing the tools and asking for changes in relation to this marketing. There is no business glue, and EPA would be substantively more effective if they integrated marketing techniques into their processes. Dr. Somasundaran mentioned the five regions participating on the one project, and asked how and if they should be further involved at the state level. Mr. Hillger replied that the states would be more than happy to participate if they were invited, and there just needs to be increased marketing from ORD to states, as there is currently none. The commentary and questions on the presentations was brought to an end.

Public Comments

Ms. Fleming announced there are no public comments.

Wrap Up and Adjourn

Dr. Somasundaran asked the group to please send their write ups to Ms. Fleming. Dr. Solomon thanked the committee members who wrote some of the report the night before. She stated they could meet as a full subcommittee the next morning and record the major recommendations for both programs, including both general overarching comments and specific charge question responses. She emphasized that if they did not talk about it as a group, it could not be included in the report. She asked the group to work on refining or adding any additional points and topics of conversation for the next day that night. She wanted to make sure they reflected on the major issues discussed that day. Ms. Fleming distinguished between private versus public meetings, and mentioned the small breakout groups the next day would not be a public meeting under FACA. Dr. Solomon asked for an effective full group discussion the next day so the breakout groups would know the main subjects to topic and write about in their response to the questions. Dr. Beamer asked if charge questions 1–3 applied to both programs and if they should write up the report separately for the programs, which Dr. Solomon responded that they did want separate reports for CSS and HHRA. Dr. Bahadori wanted them focused on the findings and the recommendations, and not necessarily provide a narrative as they are only writing a meta-report. Dr. Solomon asked the group to be brief, as having 40 different recommendations is less helpful than having 3–4 strong recommendations. They discussed the distribution of an example report before breaking for the day.

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Thursday, October 8, 2015

Subcommittee Group Discussion of Preliminary Findings and Recommendations
Subcommittee

Dr. Somasundaran recommended the group take a few extra minutes to look at the provided findings and recommendations page. There was some group deliberation over this and the group looked over the comments provided for a while. Dr. Somasundaran brought the group back together by stating there are a lot of commonalities found. Dr. Klaper responded by saying it seemed that they have made a lot of good headway, although communication and interaction with regions and programs still needed to be improved, even if they were mostly translation, time, and money problems. Dr. Bahadori asked if anyone had any additional questions for them. Dr. Klaper brought up the notion that ecology should not be divorced from these studies as it is an important component of the CSS portfolio. Dr. Bahadori remarked there was a part in the StRAP referring to cross-program integration and she would note the recommendation. Dr. McPartland asked, in reference to the research arm of ORD with most of the ecology portfolio under it, does that arm interface with CSS and the NCCT program. Dr. Bahadori responded it is starting to interface, but the areas that focus on ecological worries and stressors study them aside from chemicals. CSS works closely with SSWR and SHC, and they have an ecological focus, but not an ecological-toxicological focus. The toxicology side is part of CSS. These boundaries are hard to draw because for a while ORD's ecological portfolio shrunk. SSWR is starting to look at toxins in ground and recycled water, in order to collaborate with NCCT.

Dr. Stevens suggested they organize breakouts and focus on key questions in order to conserve time. Dr. Somasundaran responded by calling those who had pressing comments to make them before they move on. Dr. Beamer asked for clarification about the matrix diagram, as there was no check mark between life cycle and environmental justice, and she thought it deserved at least one check mark. Furthermore, with respect to feedback from regional partners, she wanted to know how exposure factors are being updated and if there was an effort to increase the certainty and confidence in those factors. Dr. Weisel remarked, in regards to listening to the regional offices, he did not hear anything about exposure, Expo-Box, or HERO, which were highlighted in the other conversations, and recommended the integration there be boosted.

Dr. Solomon thought it might be helpful to go through each charge question and distill out some key points for each one. The group started with charge question 1, as it had the broadest base of discussion since it covered both programs. She asked if they felt comfortable with the recommendation that both programs are positioned extremely well, as a lot of people were impressed. Dr. Stevens responded that he was on board recommending the program was planned and organized appropriately, but he would criticize the objective to make good progress and ask that the objectives be made more specific. Dr. Solomon commented the group should start by saying yes and then go on to talk about some of the alerts they had concern over. Foremost of the problems, there were IT issues which seem to be the largest barrier. Components of that issue include web development at the Agency level, difficulty recruiting good IT staff, and difficulty with contracting. Distinct but related to the IT issue were concerns over the budget which have impacted the ability to travel. Furthermore, potential topics to discuss included adding more formal evaluation metrics as well as creating roadmaps between and among tools to guide users.

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Dr. Solomon asked if anyone had any more key points to add. Dr. Somasundaran emphasized some of the points made could also go under other charge questions. Dr. Stevens asked for the inclusion of the recommendation on defining specifics of a scientific roadmap around the achievable goals within the timeframe. With such an ambitious CSS program, he was adamant that specific and understandable goals were essential and a critical third point. Dr. Weisel mentioned the integration of tools together, which is another aligned area to enhance overall integration. He insisted this integration needed to be emphasized in a formalized way, as forcing people to work together is often one of the most difficult tasks to accomplish. Dr. Vorhees also insisted on a roadmap, and brought up the roadmap mentioned in the StRAP for children's health. Dr. Bahadori answered this inquiry by replying the roadmap Dr. Stevens had referred to was within the CSS program for four topics that cut across all ORD programs. Children's environmental health, climate, and environmental justice are all cross-cutting issues across the six national programs in which integration is key. Dr. Vandenberg stated the fourth roadmap was nitrogen. Dr. Johnson commented about the sequence of deliverables, and how, in a large program, these deliverables will fall in different time scales. These differences in range are an important element to evaluate when considering a program. He asked to know the actual deliverables to be validated by the program as well as proofs of concept within the 2016-2017 range. Dr. McPartland pointed out the charters were organized around different research areas, and within those areas are specific information such as dates and outputs. These research areas need to be compiled along a timeline, which would help illustrate how they build upon each other chronologically. This view would be another lens through which to examine the charter objectives.

Dr. Solomon summarized charge question one and encouraged the group to take the text they already had and add points including: strong language on being impressed with the research, emphasis on the budget and IT issues, and mention of the scientific roadmap concept with sub points. This summarization could end with Dr. Weisel's call to continue efforts of integration and a note on the issues of that continual challenge. Dr. Stevens wanted to reinforce Dr. Weisel's comments, by including a comment on the training and communication needed to promote that integration. He wanted articulation of specific request points, such as what an AOP is and how it should be used. Dr. Beamer ended the discussion on charge question 1, saying scientists needed to be trained in these new behavioral aspects, which is a science and model in and of itself.

Dr. Solomon prompted the room to move on to charge question two and three simultaneously, as they are highly related and examine both CSS and HHRA. She asked the group to start with relaying some strong positives of the programs, for which they heard great feedback about the day before. Some particulars to highlight included: Connectome and Risky Business meetings, technical support, emergency situation support, and travel support. She said they needed to bolster commentary on the challenges and areas for improvement. She asked the group what the major highlighted area to address should be, beyond further integration and involvement. Dr. Klaper mentioned she had written a few areas of improvement down, such as recommending scientists directly contacting programs on how to make their interfaces personally useable so that they understand and are capable of using the tools. This change would not require augmented traveling, only an increase in educational activities, and would include more communication in the direction from the partners to HHRA and CSS instead of the other way around. Dr. Solomon

wanted to include RapidTox in the report, as the program rearranged its priorities in response to feedback from partners.

Dr. Klaper suggested they highlight that researchers are asking what they can do to make their tools better, which is a good active process. Dr. Somasundaran added there was a call for more communication and cooperation between the regions and between the regions and ORD. Dr. Bahadori clarified that chemical regulations are implemented in Washington, and the programs engaging the regions to advance the science in subjects like RapidTox is met with great resistance from the capitol, which is why they frame it as green chemistry or alternative assessments.

Dr. Klaper asked how they should phrase their comments on overcoming this issue. Dr. Bahadori replied that they needed to create a mandate to enable the regions to participate in this path forward. Dr. Somasundaran remarked some of the regional issues truly are only for that region, to which Dr. Bahadori wholeheartedly agreed. Dr. Vandenberg pointed out some of this regional work was much more of HHRA's work than CSS and Dr. Solomon resolved they would address them separately in that section. Dr. McPartland asked, when Dr. Bahadori says resistance from Washington, what level she was referring to. Dr. Bahadori said most controversial chemical regulation has been strategically controlled and deployed from Washington, and regions typically play no role in chemical regulation unless there is a spill or explosion. States play a role in chemical regulation, but regions do not, as the Agency does not want the regions to get ahead of the game. For example, if the OCSPP has not agreed to use CSS tools in chemical evaluations, then CSS cannot peddle them to the regions. Instead, they can make them publicly available. CSS cannot strategically get ahead of OCSPP in chemical regulation, especially as TSCA is being reevaluated.

Dr. McPartland commented about partners, asking to what extent CSS, and even HHRA, anticipated wanting to have regions sophisticated with these tools and dashboards versus relying on the programs to give them the results. Dr. Bahadori said their recommendation was perfect, but not in this context of boots on the ground chemical regulation. CSS needs to use partner's input to shape the tool's interface, but not to tie it to regulation. Dr. McPartland argued for as much training as possible for the regional partners. Dr. Vandenberg quickly commented that the lack of assessments is a critical issue because everyone is grasping for straws. OCSPP has the specific and unique challenge of evaluating thousands of chemicals. There are other organizations concerned with the evaluation of chemicals that also want the tools, but there is a specific issue with OCSPP and TSCA renewal. Dr. Weisel wanted to properly frame the response to ensure the training occurs.

Dr. Stevens believed, in regards to charge questions 2 and 3, the regions received great responses from CSS and HHRA, but remarked the functions seemed independent. If screening values and points of departure are needed for the two programs, cross-fertilization would produce more defensible values. He asked how CSS could produce that effect, of more defensible values, over the next 3–4 years. Dr. Bahadori replied they were aiming for 1,000. Dr. Stevens wanted a specific response about the synergy between HHRA and CSS at the regional level. Dr. Vandenberg commented there are certain particular projects and paths that relate exactly to that synergy. Dr. Stevens stated they needed to distinguish between HHRA and CSS. He felt that when individuals or regions needed a solution or assays in order to make a specific measurement,

then CSS was critical, but if they needed to examine a chemical and produce an answer the HHRA was critical. Dr. Bahadori commented the distinction was incorrect, as there are current HHRA products that are legally defensible, both high tiered and low tiered, and are part of the business of that agency. CSS is trying to create a transformation and a collaboration. The collaboration between the two programs in two new pilot programs only has region engagement from the enthusiastic Region 8 with relation to OSWER. CSS is going to see if they can generate defensible values that HHRA can then use in assessment exercises. The initial response CSS received, when reaching out to work with Superfund, was no, as they wanted lawyers in the room just to talk. However, when they expressed and advocated that the application goes beyond Superfund, as it addresses chemicals for which there is no current data, they were able to find individuals at least willing to come to the table to talk. It is a pilot exercise, so they are not sure where it will go, but the resources and effort redirected to the project in order to make it happen were large. They want to get the numbers out to the public and show how the process works. Dr. Stevens said she was describing barrier issues. Dr. Bahadori answered she was describing overcoming barriers. CSS knew if they put resources into it, and used their 12 month window of having two political appointees that supported the project, they would have an opportunity to deliver on it. Dr. Solomon commented the group does not want to get into this level of detail in their report, and she would suggest they say they think the tools, at least on the CSS front, have potential value for the regions for emergency response support and a variety of other purposes, and leave it there.

Dr. Vandenberg mentioned one of the issues for HHRA in terms of charge question 6 is how to characterize the utility of the new types of data coming in, which might relate to the issue they were already discussing for charge questions two and three. The situation is a case where the group is coming at where they have the linkage to apical endpoints, which is suitable for most of their program clients. Their approach is connecting the pieces of the endpoints. For HHRA, there are some cases that point to a subset of chemicals where they have in vivo data to work with. CSS does not have that, and so there is a whole other world of challenges that the program is trying to work through with a variety of sophisticated approaches. There is a connection here between CSS and HHRA and comments will help frame the direction that might be most suitable to recognize opportunity and deal with characterization and confidence building. Regions want to know how confident they can be. Risk assessment is not a monolith, and different levels of information might be suitable for different applications. CSS and HRRA approach the same problem in two different ways. Dr. Bahadori added the projects co-leads for the RapidTox project are Dr. Lambert, a risk assessor from NCEA, and Richard Judson, a computational scientist, and this is a CSS approach to making sure these things remain tethered together and do not spin off into their own universe. Dr. Vandenberg noted they had several staff members whose time is split between CSS and HHRA, which is a point of intersection between the programs. Dr. Somasundaran agreed with Dr. Vandenberg, and wanted the group to provide valuable comments on how to clear this minefield. He then suggested it was time to start looking at charge question 4.

Dr. McPartland quickly summarized that a lot of the discussion on these charge questions centers on scientific confidence building and deciding what measures are necessary to build that confidence. In reference to low hanging fruits, she pointed out that they do not have much to lose and should use the data they do have available, even if it is not complete. Particularly for IRIS, if

they would just take a data rich chemical going through IRIS and append a section to it, that would be incredibly helpful for building confidence, particularly in the scientific community. Furthermore, it would help relieve resistance from OCSPP. Dr. Vandenberg brought up the NexGen program in relation to this approach, as the program takes well understood chemicals and works backwards to figure out how to understand the interpretation of other kinds of data, especially for the chemicals where they have anchoring in human data. This method is not the only way to approach it, and they are approaching it from both directions. Confidence building, characterization of utility and characterization of uncertainty is a critical part of that first application in many of the programs.

Dr. Somasundaran moved the conversation to charge question 4. He mentioned the question involved complex system science, and they needed to discuss the comments on mixed systems, life cycle analysis, and chemical evaluation. Dr. Solomon agreed there was a lot to say about question 4. On the topic of complex systems, the key points of discussion were tipping points, AOP validation, and examining other species in the context of complex system evaluation. She also mentioned the earlier suggestion of performing a case study on the economic benefits of a regulation.

Dr. Waters suggested, for developing case studies, they could benefit by working backwards with the regional partners to determine the public health issue and demonstrate how something other than apical endpoints could be used in the analysis. Dr. Solomon agreed this was an interesting point to include. She also added there were fewer points made about the life cycle analytics issue, and one of her concerns was the link to sustainability as well as the link to environmental justice in a life cycle context. Dr. Klaper mentioned the comments on disposals, to which Dr. Solomon did not see a clear suggestion that went beyond what was already being done. Dr. Leszczynski mentioned they had not really discussed the issue, and Dr. Solomon agreed they could take the time to further discuss the topic. Dr. Solomon commented on discussing chemical evaluation, testing metabolites, a more dynamics approach to assays, and questions around exposures and the degree to which the exposure side is keeping up with the toxicological side. Dr. Bahadori asked if those exposure comments were to be more directed to HHRA, as the charge question was focused on CSS. Dr. Weisel commented he had exposure questions for CSS as well. Dr. Bahadori asked them to be clear in their recommendations to which program they were referring to. Dr. Solomon mentioned the suggestion for both organizations to more systematically fill in gaps in chemical space that have been screened in order to help with modeling. Dr. Somasundaran added, since there are so many chemicals, how can they screen for looking at the structure property relationships, as they cannot look at the whole population.

Dr. Weisel brought up issues about exposure research. He mentioned, in references to examining the posters, most of the STAR financial grants were given to toxicological research over exposure research. One toxicological grant was given as much money as all the exposure grants combined. Dr. Bahadori asked him to understand that those are the major technology centers, which is why they receive a substantive amount of the resources. Dr. Weisel simply wanted to point the discrepancy out and initiate discussion on how to incorporate exposure research into ExpoCast. Dr. Vorhees discussed the CSS dashboard, which had plots graphing toxicity and exposure information together, and where exposure predictions were positively below

toxicological values. She then asked if some of the exposure work in the HHRA program could be found in the CSS dashboard, to which Dr. Bahadori responded in the negative. Dr. Hubal cited all the information in the CSS dashboard as being chemical-specific, meaning that all the product categories in use and exposure estimates developed using ExpoCast are tied to chemicals. HHRA studies exposure factors, but specifically in relation to age, lifestyle, or another factor, and not to a chemical.

Dr. Vorhees wanted clarification if 100% of the CSS dashboard is in the CSS program. Dr. Bahadori responded that the dashboard resides in CSS but contains any toxicological data produced by the broad scientific community that has been annotated into the system by CSS, and draws on exposure data when available or estimates it. Dr. Vorhees clarified, for the purpose of this evaluation, it is 100% in CSS, which Dr. Bahadori agreed with. Dr. Bahadori added that the only part of HHRA that they are evaluating for this charge question is the project numbers they see in the agenda and the two project demonstrations they saw, as everything else was CSS.

Dr. Stevens thought thoroughly about chemical evaluation and had evaluated the area was clearly moving from high-throughput screening concentration values to exposure based, in vivo, points of departure as the program key. In regards to the complex systems and chemical evaluation aspects of the charge question, looking at the last decade of creation and implementation, there is always skepticism towards new ideas. Examining how to move from in vitro concentrations to in vivo risk assessment, as well as including complex systems in the analysis, is a positive movement forward, as it informs the researchers exactly what they need to do in order to be successful. He then asked the rhetorical question of what the complex systems initiative, from its early inception point, learn from high throughput screening in terms of data quality, the data needed, and specific objectives, and how can they position themselves for success relative to it. He believed the chemical evaluation program overall had been successful, and have moved to a point where they have the opportunity to provide points of departure as defensible data. He also asked how the organizations deal with complex systems, as they are an order of magnitude more difficult for people to absorb. He asked if the subcommittee would add these recommendations, which they happily agreed to do.

Dr. McPartland talked about increasing the chemical space being evaluated, as she wanted to put a plug in for increasing the biological space. CSS is the lead in ORD for the Children's Environmental Health roadmap. Biological space is such a pressing issue for children's health, and there have been great examples where CSS has responded, such as the biological gaps for thyroid hormone activity. It would be helpful for CSS to have a similar continual review of that critical biological space, particularly with regard to leading Children's Environmental Health. Dr. Bahadori said the thyroid study went into high throughput, but developmental toxicity studies are a whole other area they are developing assays for, at a more medium throughput. They are currently evaluating and beta testing these assays. They are unsure whether or not it will be successful enough to put into ToxCast, but they wanted to compliment ToxCast with medium and low throughput assays. Dr. Somasundaran alleged there was discussion on whether or not high throughput work accurately represents real systems, especially in terms of nanoparticles, and suggested they show how high throughput research truly relates to real systems. Dr. Solomon recommended it would be helpful to point out a set of challenges that persist in the program, as well as areas where the program has taken steps to try to address some

of these challenges. Furthermore, these challenges around neurotoxicity and the thyroid might be good to point out. She hoped people were thinking about which breakout group they wanted to contribute to.

Dr. Solomon initiated discussion of charge question five. She asked, specific to CSS, should they include charge question 5 conceptually with the charge questions around partner interactions or the creation of tools, or should they be kept separate. Dr. Somasundaran wanted them kept separate. Dr. McPartland believed they should emphasize and repeat important points, as she also put IT issues under this question, but they should not necessarily combine the questions. Dr. Klaper remarked that Dr. Beamer did the same thing. Dr. Bahadori agreed with the merits of repetition and emphasis. Dr. Leszczynski believed they should highlight here the comments over whether or not the Agency did enough to make the information public. Dr. Somasundaran agreed with focusing on the topic of knowledge delivery, as the public does not know about most of the valuable work at CSS and HHRA, and they agreed to add a paragraph on that topic. Dr. Beamer remarked the topic of the time to learn about tools should be incorporated into the planning tools discussion, especially in regards to underestimating the tools and resources necessary.

Dr. Vorhees mentioned, related to IT issues, when people access information on the website, it is hard to see what the latest and highest quality information is, which be helpful to the general public. Dr. Bahadori replied the whole website underwent activity where they mushed up all the information and made the website information at a third grade reading level. CSS needs to figure out a different way to communicate their material to the scientific community, because the website has a third- to fifth-grade reading level, which sections reaching an eighth-grade reading level at maximum. The low reading levels degrade the website, as then all the website says is "lots of chemicals and need to study them," which is the entire program. Dr. Vorhees said she had clicked on risk assessment tools and then databases, and Expo-Box was listed below the 1997 *Exposure Factors Handbook*, which is confusing to users. Dr. Vandenberg responded they were switching systems that month, and there were a lot of broken links. Dr. Bahadori added in they were switching to Drupal. Dr. Jarabek added the migration was stimulated by wanting open access to a lot of things. The site is under construction temporarily, and Dr. Vandenberg commented the renovations were only for this week. Dr. Vorhees said her comment would be to organize the site in a way that the public can understand how the information was prioritized, including the partners, contractors, risk assessors, and fellow government employees in the description of public.

Dr. Stevens wanted to focus on the IT issues a little more before they moved on to charge question 6. He remarked that IT has multiple dimensions, and they want their recommendations to be meaningful. There are three bins of discussion, one of which covers what the external face of the EPA to the public should look like. The second bin is about CSS having new computational power and capabilities. The third piece is under HHRA, and that is a critical barrier to the sharp end of risk assessment and relates to the amount of information being handled and the manual curation of that information occurring. He asked what they thought about all agencies funding environmental research putting their information into a common data format, which would remove the manual curation aspect on EPA for that data. He commented there would be resistance to this change, but that they really needed to wrestle with the concepts of these three bins. These issues are a huge gap in IT infrastructure, as it is a defensibility issue,

and made the analogy of a 900-pound gorilla around data management. Dr. Solomon mentioned the she wrote down the third bin discussion topic under charge question six, as it is specific to HHRA and is also a legacy data issue.

Dr. Solomon moved the conversation to charge question 6. She had flagged the issue of acute or shorter term RFCs or RFDs, which they might want to temper by saying when data are available and appropriate, as it is not appropriate for every chemical or dataset. She believed they also might want to comment on HERO, Expo-Box, and BMDs. Dr. Johnson believed charge question five should be defined as a two-way street, so fit for purpose translation and knowledge delivery should be viewed as coming in and going out. Dr. Bahadori believed the case study achieved that. Dr. Solomon remarked charge questions 2 and 3 clearly had to do with partner involvement and responsiveness, and they would definitely want the incoming there, but the charge question 5 fit-for-purpose language focuses more on going out, although it does get to the idea of whether or not it is relevant to what the needs are. Dr. Johnson stated there is technology coming in, shared technology coming in, and collaboration with groups with incoming data, and legacy data information needs to be brought in at some point.

Dr. Leszczynski had comments concerning charge question 6, but that were directed more towards CSS than HHRA. His comments were about data for computational methods in order to improve confidence and capacity. There were a lot of demonstrations given of methods to characterize thousands of compounds, but this was basic stuff that was not accurate, as there are too many compounds to accurately do a low throughput analysis. However, nowadays, compositional chemistry methods could provide an accurate approach to the characterization of these compounds, and he felt that he had not seen an effort to incorporate these approaches. Dr. Bahadori responded there was not an opportunity to make a poster about it, but that in the past seven months they have hired several, prominent, compositional chemists to begin assessing the program and to begin to link compositional chemistry tools to all the other work CSS is doing. However, CSS has just started bringing these people into the work, so they presently do not have anything to show for it.

Dr. Leszczynski acknowledged the hiring of these researchers was an important step forward. Dr. Bahadori asked for that recommendation to be recorded. Dr. Somasundaran supported the use of computational chemistry to build the foundation for the studies, even though it still would not give predictive capabilities based on the structure. Dr. Leszczynski rebutted that it would be possible with a lot of resources, to which Dr. Somasundaran responded that there were enough computational chemistry tools available now to start building that foundation. Dr. Klaper asked about the CSS definition of sustainability and its role in the programs. Dr. Bahadori remarked sustainability was only included in the title because of Dr. Anastas, as all of the EPA organizations except HHRA have sustainability included in the title, since it goes across all programs. The CSS piece of sustainability centers on avoiding unintended consequences. The other part of CSS sustainability is enabling changes without harming future generations, and they are involved in what they can contribute to in regards to sustainability but are not necessarily involved in the economic benefit analysis side of it. Dr. Hubal brought up that their focus is on critical indicators of sustainability, more than the economic piece, as if they do not do this analyses than no one would. Dr. Somasundaran remarked hearing that “green” is out, with "sustainability" in, meaning the incorporation of economy and societal values into analyses.

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Dr. Beamer asked HHRA if they could clarify what response they were looking for between charge questions 1 and 6. Dr. Vandenberg replied charge question 1 deals with the overall framework of the program and how it is structured to address Agency needs, while charge question 6 zooms in on a specific area of emerging science and asks how to interpret and evaluate it, especially in regards to its limitations, strengths, and uncertainties. They would benefit on comments in terms of opportunities and directions they should take in relation to this emerging science. Project 8 has a lot of this work described, especially 8.4, and they are trying to structure their program to address all the needs and opportunities appropriately. Dr. Beamer wanted clarification that charge question 6 was solely focused on new and emerging science. Dr. Vandenberg replied that was their intent. Dr. Stevens asked if they had enough power in computational biology. Dr. Bahadori responded they were hiring in that area, as they have a couple of senior positions there, but wanted to make at least three more senior positions dedicated to computational biology. Dr. Weisel wanted an answer from Dr. Vandenberg about his first question over HERO and Expo-Box, and Dr. Vandenberg pointed him towards Project 8.4.

Dr. Somasundaran ended the discussion and asked if there were any volunteers for each charge question. Dr. Solomon hoped that people would started to break out into small groups or by themselves in order to write parts of the recommendations. The subcommittee discussed how to best break out into groups. Dr. Solomon said they should use what was written for each question in their discussions and to weave it into the report. Dr. Stevens asked if they could do a quick run through on charge questions 4, 5, and 6, and then come back and roll those into questions 1, 2, and 3. The group decided against this suggestion and decided to keep the charge questions separate. They then deliberated some more on how to breakout and individuals volunteered for charge questions. They decided to structure their input in sections over the strengths, challenges, and areas for improvement in the programs and to present their recommendations in condensed paragraph form.

Subcommittee Breakout Group by Charge Questions – Discussion and Writing
Subcommittee Breakout Groups

Charge questions 1 and 6: Dr. Solomon, Dr. Weisel, and Dr. Leszczynski
Charge question 4: Dr. Johnson, Dr. Waters, Dr. Klaper, Dr. Stevens, Dr. Somasundaran
Charge questions 2, 3, and 5: Dr. McPartland, Dr. Beamer, and Dr. Vorhees

Discussion of Outstanding Issues, Review of Draft Report, Review of Timeline and Assignment of Follow-up Activities
Subcommittee Breakout Groups and Leads

Dr. Somasundaran brought the group back together, and Ms. Fleming started the discussion by clarifying the FACA rules. E-mail discussions and deliberations involving half the subcommittee or more are open to the public. They want to have deliberations open to the public for any teleconferences and other meetings. Google documents, emails, and phone calls are fine to be private in small groups, but must be public if in bigger groups. As long as small groups are five people or less, then their discussion does not violate FACA by being private. She suggested they should identify one person as the point of contact who can send all information to the chair and

vice chair, as well as cc herself. The vice chair had volunteered to compile together the BOSC report pieces. Dr. Stevens asked about a hypothetical situation. Ms. Fleming clarified any part of the meeting is public record, including the meeting summary notes and draft text, and could be obtained by request. The meeting notes will be posted on the website once they are vetted and approved by the chairs. She added, in terms of the timeline, the chair and vice chair have decided to have a follow-up teleconference, which will have to be announced in the *Federal Register* as a public meeting. Dr. Solomon recommended they block out two hours for the teleconference. Ms. Fleming said she would send around a poll for people's availability. Before the teleconference, she will have a draft of the BOSC report for them, compiled by Dr. Solomon, which will be the pre-meeting material in public record that they will discuss during the teleconference.

Dr. Solomon was not sure what to set the timeline as, since she was not sure quite how far people got in their discussion and write ups. She asked when the whole document needed to be submitted. Ms. Fleming responded it was due the week of November 17, as the BOSC Executive Committee is going to meet on December 8 and wanted a draft at least three weeks before the meeting.

Dr. Solomon set the teleconference for the week of November 2, in order to have a few days afterwards to make the necessary additions and subtractions needed before turning the report in. She set the date for sending the draft out to committee members the week of October 26, so they would have time to prepare, and therefore asked the committee to turn in the materials the week of October 19 so she would have time to compile the notes. She clarified this timeline meant individuals would have 10 days to get their drafts together and sent off, to which members nodded in agreement. Dr. Solomon explained, during compiling, she would not only put the pieces together, but would also reference her notes to make sure they captured everything, tighten and trim the sections, look for unnecessary redundancy, and smooth the paper over so it has one uniform voice throughout. She asked the committee if they were fine with this revision mode.

Dr. Stevens mentioned their group specifically had discussed each going back through the documents and seeing if anything was missed. Dr. Waters believe once they did those revisions amongst themselves, they would have a good draft, and Dr. Stevens added then Dr. Solomon would not have to look for any missed information and could focus solely on coherency. Dr. Solomon accepted this proposal. Dr. Stevens asked if any other group thought about performing this revision themselves.

Dr. McPartland asked for clarification over the time points in the week of format, and Ms. Fleming asked for a reiteration of the timeline checkpoints. Dr. Solomon responded the rough deadline for workgroups to turn in their reports was October 19, which will be returned as a draft around October 26. The teleconference call will be either the week of November 2 or 9, and the final document will be sent to the full BOSC by November 16. Dr. Vandenberg reiterated the subcommittee could not directly connect with him or Dr. Bahadori for questions, and they would have to go through Ms. Fleming, who asked if they would participate in the conference call. Dr. Vandenberg responded they would be able to, but would only speak when asked a direct question, and not engaging like they have in the meeting the past two days. Ms. Fleming felt the teleconference would be an opportunity for the subcommittee to go over large overall findings

and hit the main points and ask the program representatives if they got it right. Dr. Vandenberg remarked they would also send comments in advance on the draft through Ms. Fleming.

Dr. McPartland wanted to ask Dr. Bahadori about question 5, as her group was uncertain what was being asked in the question. Dr. Solomon replied Dr. Bahadori would come back to the discussion around 2:00, and they could ask the question then. Ms. Fleming commented, before they jumped into discussion, she had two logistical points to discuss. The first was about flash drives, telling the committee they could keep them if they wanted to, otherwise they would be recycled by EPA's meeting contractor, ICF. The second point was about mailing the big binders, and if they left their binders on their desks with their name plates on top, ICF would collect them and ship them off to them.

Dr. Somasundaran opened up discussion, and said they were going to go question by question. Dr. Solomon had added a few points to each section, and remarked several people had written strongly worded text on the IT issues, and she included it all which made the section a little too long, and asked to share it with the subcommittee. Dr. Beamer asked if the response was still a joint effort. Dr. Solomon responded she wrote the answer to this question, but other groups should give feedback. She wrote it as a crosscutting response and then examined CSS and HHRA individually. Dr. Beamer agreed it would be helpful for crosscutting issues and people took time to read the paragraphs. Dr. Stevens suggested an edit so all the specific conversation about IT would be captured. Dr. Solomon replied the points were somewhat different and she had previously bulleted part of the section. However, she had to cut it because it addressed hiring people, contracting IT support, laptops that can handle the big data that these programs use, and the Agency rules that limit how material can be prepared for the website, which she thought was too much to include. Dr. Stevens asked if the response captured the conversation they had over the data and tools HHRA provides. Dr. Vandenberg responded the response addresses that nicely. He also clarified that the Agency requirement about website as grade-school reading level is not really a legal requirement so much as the organization wanting the use of what they deem plain English. Dr. Stevens commented item two is HHRA specific, and then asked Dr. Solomon if she heard if question one was more CSS specific and question two more HHRA specific. Dr. Beamer wanted them to focus on the content of the document while they were all together. Dr. Weisel commented he was not sure what question two meant. Dr. Klaper asked if being forced to use plain English was an IT issue. Dr. Vandenberg commented it was more of a communication aspect, and Dr. Solomon asked if it should be moved. Dr. Klaper wanted the bullet to be moved to the translation to the public section instead of the IT section, as it is more of an issue about trying to communicate technical concepts to the general public.

Dr. Klaper remarked she liked the proof of concept, which echoes some of the things they had talked about and gathered general consensus. Dr. Solomon asked if the ambitious nature comment was specific to CSS, and if proof of concept was more CSS and HHRA. It was confirmed by Dr. Johnson that proof of concept was more CSS specific. Dr. Solomon mentioned the case studies could apply to both CSS and HHRA. Dr. Stevens commented he was perfectly fine with condensing the sentences. Dr. Solomon loved Dr. Steven's section about interdependencies and tradeoffs, and wanted to make sure it was included and framed correctly under question one. Dr. Stevens remarked the virtual tissues, new assays, and AOPs were all integrated appropriately, but examining the charter document and the deliverables and timeframe

mentioned, there were too many interdependencies and this is something of a problem. Dr. Solomon commented she would keep those points in this section, and then talked about the report areas covering scientific roadmaps and integration of organizational change.

Dr. Stevens asked what they were looking for around the organizational change concept. Dr. Beamer responded they included comments on how to make the process more effective from problem formulation to translation to evaluating effectiveness. Dr. Stevens added, to him it means using technology to perform tasks in a different way. However, that is only part of organizational change, which also encompasses technologies, tasks, and organizations, and addresses cultural and behavioral issues as well as technical issues. Dr. Beamer wanted that articulation included. Dr. Solomon wanted to use the broader framing of question one to express these programs are trying to catalyze broader organizational changes throughout the Agency, which is a difficult and lengthy process that needs to flow from beginning to end. Dr. Beamer remarked they did not want their recommendation to be just another layer of onerous bureaucracy, and it instead needed to be a transformative and positive influence.

Dr. McPartland asked if the report was being framed as a context setting for all the goals of HHRA and CSS, or if it was being framed more as general recommendations. She did not want to suggest CSS and HHRA surmount legal structures to try to fix some of the recommendations. She commented on trying to blend into the organization versus making the organization work for them. If they are providing recommendations, rather than describing an opportunity for BOSC to communicate challenges in the growth of these programs, then they need to be careful. Dr. Stevens replied they were specifically addressing the kinds of interactions between the regional offices and CSS and HHRA in terms of organizational change and how they can translate research so it can impact the specific tasks that are being performed on the front lines of risk assessment. He felt addressing these issues seemed more achievable within the sphere of influence within CSS and HHRA, and the subcommittee needed to be clear about what is in the scope and what is out of the scope of the programs, which Dr. Bahadori and Dr. Vandenberg had repeatedly expressed. Dr. Somasundaran suggested it was more of a coordination than an organization issue, which Dr. Vorhees cited was part of the next question and suggested they move onto it. Dr. Solomon agreed they should move on, and said she would email the introduction and feedback around and incorporate any additional comments into the response for question one.

Dr. Solomon asked if anyone from the subgroup wanted to come talk about charge questions 2, 3, and 5, and the group decided to talk through the points. She asked the group still had a question for Dr. Bahadori, and they said they would wait until they got to question five to ask it. Dr. Vorhees stated her group organized the topics into three general categories of strengths, challenges, and areas of improvement. Question two was about the involvement of partners in problem formulation, or how well partners participated in research planning effectively. There were many strengths. The comments, in general, applied to both CSS and HHRA. They shied away from talking about budget constraints, understanding of EPA's budget, and commented what they would need to do to make the essential face-to-face meetings happen. The rest of their commentary in the written report was self-explanatory.

Dr. Klaper suggested they separate out the program offices and regional offices as being two separate types of clients. Dr. Vorhees replied the comment should have read Project 7. Dr.

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Beamer asked to explicitly separate out the experiences and statements of the program and regional offices and Dr. Klaper wanted it noted they are both positive. Dr. Weisel wanted it included that CSS and HHRA actually listened to feedback and incorporated it, as shown by the STAR grant, and Dr. Solomon talked about including examples of informal contact and technical assistance. Dr. Beamer stated they interpreted question two as how CSS and HHRA received input, and question 3 as how they addressed that input. Due to this interpretation, their group had not gotten to discuss the informal communication yet. Dr. Vorhees commented to keep going, they just wrote them down, and it could be included in the full report. Dr. McPartland believed they fell into two categories, one to assess effectiveness points and the other to express value of continuing direct interactions with federal partners. Dr. Vorhees specified her group spent a majority of their time discussing ORD's communication with the regions, and how ORD reaches out to partners in research planning, and asked the organizations to formalize a step where ORD asks partners what resources and products they need to come out of research programs. Dr. Beamer had specific thoughts on this process formalization, including noting how many of the partners are being reached, a metric of knowing that the correct people are being reached, and making problem formulation as a part of their job. This formulation could be seen as a daily scope of work instead of additional work. The recommendation is more of a challenge than improvement. She also emphasized the importance of the cross-office details and getting regional staff to go to ORD and work with them directly, which would possibly be constricted by the budget, but would be highly effective. Dr. Stevens mentioned proof of concepts create incentive, meaning when a person sees something solved that they could not solve before, then they are a part of a subgroup of individuals that value the same things and tell people all about their great results and stimulate the change. In relation to this concept, he asked, in terms of the 10 regions, is there a way to focus on one specific question per region depending on what is most important to them. There should be an incentive created to promote this shift. This would be a strategy to increase these interactions by focusing on one problem for each region that is aligned with CSS and HHRA strategies. Dr. Beamer thought this topic might fit better under charge question 5. Dr. Stevens, in reference to shifting the way people work, believed there needed to be an incentive put in place to induce them to make that shift, so that the employees have the "I get more out of what I already do" mindset instead of the "I have more to do" mindset. Dr. Solomon liked that idea, and was not sure if the resources were available for all 10 regions, but believed they could use a few of the regions as case studies. Dr. Stevens mentioned Duluth leading the AOP, and Dr. Bahadori pointed out Region 5 being a direct partner on that study. Dr. Stevens wanted to create the incentive to be more familiar and to contribute. Dr. Bahadori mentioned Dr. Keteles and how she had joined the RapidTox team and offered Region 8 data for that purpose. She stated, in terms of the proof of concept idea, it was the only way for CSS to engage in that manner. Dr. Stevens asserted the key point is the idea of incentives, and asked what incentives were available to entice partners. Dr. Johnson pointed out the benefits of being an early adopter. Dr. Stevens stated that in business it reduces the need for a huge sales force, because the early adopters become the sales force in the local community. Dr. Bahadori emphasized, in chemical safety, early adopters are often the ones who get burned instead of benefited. However, CSS would help early adopters digitize their data in return, so they did pay for the engagement in a manner.

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Dr. Beamer mentioned they wanted to highlight the case studies as a positive, and Dr. McPartland asked Dr. Bahadori if CSS used case studies as proofs of concept. Dr. Bahadori responded the case studies are almost always directed at regional needs, as they serve as a bridge between CSS and the regions. Dr. McPartland asked if the case studies were in the charters, which Dr. Bahadori responded in the negative, as the charters were developed 1.5 years ago and the case studies 3 months ago. However, many of the case studies were reflected in the posters. Dr. McParland wanted to highlight some of the case studies in the positive feedback section. Dr. Vandenberg discussed early adopters in terms of the Superfund technology support centers. He asserted it was variable across the regions how much they embraced the opportunity in each region. Certain exposure scenarios were coordinated with regions, but the challenge is to communicate that HHRA has the facilities to support them, and it is variable across the regions how much they recognize and respond to that communication. Dr. Beamer emphasized the daily support that goes undocumented is important to showcase. The subcommittee understands both programs are highly crosscutting, but it also needs to be explicitly said how important they both are to protecting the public's health. The subcommittee brought up the topic of budget as well as the budget slides the subcommittee had seen for CSS and HHRA. The bulk of the HHRA budget is spent on IRIS, ISAs, and provisional values. Dr. Beamer expressed it was remarkable bang for the buck, for how much they spend versus what they are charged with doing. OCSPP sold CSS well in their presentation. She asked about RARE and if it cuts across CSS and HHRA, and Dr. Vandenberg replied it cut across all of ORD. Dr. Johnson asked where the program originates from and what happens with the regional areas comments and evaluations. Dr. Bahadori mentioned the evaluations of call data by national directors either leads to adopted projects, with committed collateral resources, or the projects not being adopted, and then no funding given.

Dr. Beamer believed there were lots of areas for improvement, and she wanted to put the topic of knowledge transfer under charge question 3 for HHRA but under charge question 3 or 5 for CSS. Dr. Vorhees mentioned they had not yet talked about part B. Dr. Beamer asked Dr. Johnson to reiterate his point about partner collaboration and proof of concept. Dr. Johnson commented, when there is a situation needing a lot of communication and resources, the organization needs to create a hub for it with its own budget and head coordinator. This concept works beautifully if the correct coordinator is chosen, as it stimulates interactions. Dr. Beamer asked Dr. Bahadori if that would be helpful, who responded that a similar concept—the translation hub—was already in place and has its own resources.

Dr. Johnson mentioned the conversation yesterday about difficulties with communication and budget, and the need for one individual to be in charge of coordination. Dr. Bahadori responded they had hired two people to deal with communication, but the biggest challenge they face in terms of translation is travel expense. Dr. Bahadori asked them to include the recommendation to increase the travel budget in order to augment translation and communication. Dr. Stevens added, if CSS does not receive the travel budget, they might instead obtain a budget for creating virtual face-to-face interactions. Dr. Johnson appended that travel restricts what is possible, not just budget. Dr. Bahadori mentioned they did not lose the $100,000, but they could not use it for travel as was originally planned and instead used it to fund a post-doctoral position. Dr. Vorhees mentioned they could do more for some of the challenges they had listened to, which Dr. Bahadori agreed as they support CSS's direction. Dr. Beamer referred to the positive remarks.

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Dr. Bahadori replied they had not understood how worthwhile the expense would be to archive the webinars, as people do go back to examine the archived webinars.

Dr. Beamer further recommended training the state, county, and academic staff, in order to teach the trainers adequately the materials. Dr. Vandenberg clarified travel expense was decided by Congress' budget and they could not change it. Dr. Vorhees stated item F was IT related, because it would need IT to be implemented, and it has the potential to be exposure assessment, showing interrelatedness of guidance and tools. The programs needed to include information on the relative quality and confidence in tools and what timeframe they apply to, and need to figure out how to organize it to facilitate more efficient use. Dr. Bahadori acknowledged these good ideas and pointed out that CSS works on integrating human and ecological exposure, but are against the separation of exposure and hazard assessment, as one cannot be assessed without considering the other. They are crosscutting issues. She discussed exposure axes, kinetics, and dosimetry. Dr. Somasundaran brought up partners in the government and the participation of the southeast region. He emphasized it appears to be possible to have these connections, but maybe ORD was not involved at all in the Gulf. Dr. Bahadori responded that ORD is highly involved, but they cannot send too many people to the same meeting. There is a huge facility in Pensacola, Florida, and CSS has a project on how to do exposure evaluation post disaster to assess the resilience and recovery of the area. Dr. Somasundaran said excellent useful work was being done in EPA regional labs. Dr. Beamer mentioned the need for acute reference values. Dr. Vorhees broadened the scope of the subject to discuss a whole range of challenges that partners face.

Dr. Solomon asked the room to move to charge question 5. She also asked if the breakout group had sent their charge question 4 draft yet, which they had not. Dr. Somasundaran wanted to move to charge question 4, as he believed it would take a while, but the group decided to move to charge question 5 as it would take a while to put question 4 up on the screen and question 5 was most related to question 3. Charge question 5 was over input for fit for purpose and knowledge delivery in context of CSS. The group understood fit for purpose in terms of partners, but asked what fit for purpose meant in terms of stakeholders. Dr. Bahadori replied they held a meeting to figure out and explore how computational toxicity data can be expanded or made more useful to the community that does environmental epidemiology work, and had to address questions such as where to go in either biological or chemical space, how must the dashboard look, and are the right pieces and resources in the dashboard. After the meetings they did follow up activities with academics to see where to go next. They rolled out the dashboard to them and rolled in a lot of information on what they are actually looking for, in regards to the environmental epidemiology community. EPA, especially CSS, is always looking for molecular epidemiologists to help form an understanding of how to make the data useful. She further clarified stakeholders in terms of industry.

Dr. Beamer asked if part of CSS's goal was to communicate information and knowledge to the general public. Dr. Bahadori replied they are still not doing well as communicating with the general public, but they do interact with industry, animal rights, NGOs, Canada, stakeholders, and other governmental organizations. Dr. Somasundaran said, with regard to lack of epidemiologists, NIEHS has a lot of them and asked if they could interact with them. Dr. Bahadori responded that CSS has leveraged NIEHS, but that they do not have a lot of actively researching epidemiologists there, and instead got to NIH or the National Institute of Child

Health and Human Development. Dr. Somasundaran agreed that it was the proper way to do it. Dr. Bahadori asserted they use every resource possible and available. Dr. Beamer believed a major strength in this area was its inclusion in the solar system diagram, and recommended the next step would be making it a research in and of itself. Dr. Bahadori answered they had two hires and one fellow already researching it. Dr. Beamer mentioned the case studies and proof of concept were two other areas of strength and then thanked her for answering the questions and addressing fit for purpose. Dr. McPartland pointed out training with regards to knowledge delivery. Dr. Beamer added it applied to both CSS and HHRA, but they put it under CSS as they want to stimulate scientist-to-scientist interaction. Dr. McPartland discussed the Sustainable Future's program and asked if it would ever be possible for CSS to have a formalized program like it. Dr. Bahadori liked the suggestion and wanted the example recorded, which it had been. Dr. Bahadori wanted to explore that training, but also wanted to use the presentation input to shape training material. Dr. Beamer remarked it was not obvious where to record the "treat them as a client" idea, which they included under problem formulation, but which Dr. Vandenberg thought should be put under charge question 3 as well. Dr. McPartland asked the room if there was anything they missed, especially any partnership points that should be included but that were not mentioned. Dr. Johnson wanted the term recommendation used in the report, and Dr. Somasundaran applauded the use of the easy-to-read and brief bullet points.

Dr. Waters opened discussion on charge question 4. Her group took on 4a and 4c together, as there was a lot of synergy between the complex system science and chemical evaluation topics. They wanted to weave in all the comments afterwards in terms of what might be missing. Dr. Waters read the paragraph they had created word for word from the page. For strengths, in terms of complex system science, the CSS program is uniquely positioned to move away from hazard identification to enable more system based risk assessment. Complex system science will transform the field to move away from in vitro evaluations towards early measures of adverse response that would be indicative of apical endpoints using AOP. Translation of AOP should extend from a qualitative framework to quantitative prediction and effectively integrate high throughput analysis with risk assessment. The CSS AOP wiki concept is a unique opportunity to leverage knowledge of toxicity and risk assessment to the community. A major challenge is to build an ontology or lexicon with proper IT structure for the wiki and make it similar in structure to the Reactome database, with well-defined and searchable terminology that are standardized. CSS staff could consider working with other public database efforts to develop a community standard in the field and to leverage preexisting knowledge and experience. A good example was the structure provided on the wiki for an androgen receptor AOP, which was a great of AOP format at the multi-scale level needed for making systems predictions. Other examples were not as well made, such as the liver fibrosis AOP, which was qualitatively and anecdotally useful, but just kind of thrown on the website. CSS has great opportunity to define the standard in the field from the beginning and to transition the knowledge base from the wiki to a quantitative framework. There needs to be an effort to generate dynamic data, including both concentration and time, to enable predictions of risk or hazard in relation to dosimetry. The group recognized the computational complexity of simulating from AOP or complex systems data is beyond the 2019 timeframe. However, proof on concept through case studies would demonstrate viability of such an approach. There should be continued integration of CSS and HHRA to work backwards

from the apical endpoints to the MIE and incorporate dosimetry at the point of action and tissue dose, which will ensure greater confidence in the approach in the long term.

Dr. Waters asked for comments. Dr. Vandenberg discussed Dr. Axelrad, who does benefit work, on this topic. They are trying to determine apical endpoints that people will consistently use. Dr. Waters moved on to quickly reading about her paragraph on virtue tissue models. Virtue tissue models are important for predicting biological properties from biological activity, and therefore translate from in vitro measurements to a physical system response. The models are well poised to provide confidence in high throughput toxicity test data to successfully predict likely adverse effects of a chemical with only having in vitro data as well as potentially identifying gaps in biological space that require new assays developed. Beyond 2019, models could be used to formalize AOP. In absence of this use, they could be perceived as an academic exercise. The group's recommendation for the 2016–2019 time frame is to make a case study that demonstrates, for untested chemicals, that biological activity defined in ToxCast does translate to biological properties at the tissue level and show a connection to physiological responses in vivo.

Dr. Klaper remarked the first sentence of their paragraph was too strong and they should say that they have the potential to predict biological properties, as it is only an interesting future promise or goal. Dr. Bahadori commented that the research has already started to happen, and it helps that half of the virtual tissue group sits next to the chemical evaluation group. Dr. Vandenberg stated they mentioned biological activity, biological properties, and apical endpoints as they are purposefully constructed on risk assessment paradigm from hazard identification all the way through risk assessment. He asked if this came through to the group, and they responded that it did.

Dr. Waters brought up charge question 4c, chemical evaluation. Dr. McPartland said she still had one point to mention on 4a, which was that CSS was applying a multipronged approach to developing AOPs, but she could not see how all the approaches were coming together. HHRA, in Project 8, used disease-down approaches to formulate AOPs while there are also expert based approaches to developing AOP. She said it would be helpful, as a recommendation, to hear more about how CSS was going to link it all together. Dr. Stevens remarked this recommendation was included in the request for standardization within the AOPs and bundled into the comments about structure of the AOP wiki, such as its components at each level. Dr. McPartland agreed AOP wiki would serve as a good storehouse. Dr. Stevens said, with this call for the standardization around the wiki, they wrapped it into that one focus area because all the information derive from "what is required to deposit something?" Dr. Bahadori said there was training on how CSS is doing it, and based on the feedback, there is lots of opportunity for success but also lots for implosion if they do not standardize the process. Dr. Stevens asked the room if they thought more detail was important to add.

Dr. Klaper questioned why their comments were not included regarding the concept of the systems approach being used to feedback to design some of the approaches being used in the high throughput screening. She also asked about the missing organism part. Dr. Waters replied it was either in another part, or in another location not discussed yet, as the report was written in chronological order. Dr. Bahadori commented they were receiving the biggest pushback about adoption of AOP because of a lot of possibility for mayhem and not enough specifics in that area, and they should include those comments there.

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Dr. Jarabek wanted to expand the comment further, and said they should embed AOP diagram into biomarker and MOA schemes. AOPs will be modular and inform MOAs for many chemicals, as they are supposed to be chemical agnostic and biologically significant as opposed to nuances of dose-dependency and direction which are chemical specific, and they wanted to make those as flexible as possible and in a broader context. Dr. Bahadori clarified CSS was not talking about biomarkers, but talking about dosimetry at the appropriate level of exposure. They took biomarkers off the table because it becomes an obsession. They care about the interaction of hazard and exposure at the proper biological space, which feeds into the quantitative AOP. Dr. Jarabek said she was speaking about the translation to an application in risk assessment. Dr. Bahadori qualified it was for CSS research efforts and they want to quantify it in the biological space without using the risk assessment framework. The current risk assessment framework cannot inform a program like CSS that is future casting. Dr. Jarabek replied she was trying to show opportunities for linkage, and was not trying to constrain it. Dr. Bahadori said they can work on it between the CSS and HHRA in the future, but for the recommendation they should focus on how to make AOPs more global.

Dr. Stevens asked if they would agree that a biomarker is an apical endpoint. Dr. Klaper rebutted it depended on the biomarker. Dr. Stevens clarified that he wanted the issue able to be attacked from a bottom-up, middle-out, or a top-down strategy. He saw one of the intents of the program, as well as the comments relating to demonstrating connectivity with proofs of concept, to make a multi-scale and multi-dimensional format, with programs applicable across scales. There was a call for purposeful redundancy of this issue throughout the report.

Dr. Waters read the group's note on chemical evaluation, and commented they would rearrange the information when they finalize the paragraph. They highlighted that the ToxCast program had successfully established the biological properties and activities for unknown chemicals, which is an invaluable resource for the scientific community and is being used around the world. As pointed out in response to questions two and three, this data as had a real impact on public health practices. For example, the pesticides program is using information from it to make risk assessment decisions and response based on the information. There is a clear impact on region needs. It has moved concentration-based chemical data to exposure based predictions of biological activity and CSS is well poised to address pharmacokinetic issues. For example, it has incorporated metabolism and metabolite testing into the high throughput toxicity testing framework, which is critical new work in progress. The desire for stronger integration into QSAR model for read across and prediction of metabolism has resulted in several new hires to address that gap. The integration of dosimetry with target tissue dose and margin of exposures is key for translating that hazard to risk. Maintaining that focus in proper resourcing efforts are essential for success. Additionally, adding knowledge from complex systems science research and adding new assays will be useful for risk assessment, such as thyroid regulation assays, which will close the iterative loop across the CSS program. Translation across species is a key tool for risk assessment. The sequence path tool is doing a nice job of sequencing species for assay targets in ToxCast. The subcommittee wanted to know how this can be better used or augmented to predict structure and ultimately activity that would be necessary for risk assessment. For example, they asked, are there structural biological approaches that could be used to improve structural prediction of function and eventually potential outcomes across

species. From what they heard about CSS, there are a lot of these studies at the surface, such as structural prediction and docking, but they do not know the status of the projects.

Dr. Klaper argued they need to be more specific about the outcomes that need to happen in order for some of these things to be developed. Dr. Waters replied they need to balance these ideas with the funding, and prioritization always needs to be balanced. Dr. Klaper responded that it is not their job to determine how funding will be allocated, it is to decide what science needs to be done in order to properly answer the question. She further added that the problem they currently have is not having the science necessary to answer some of these questions, and this should be the target recommendation. Dr. Stevens asked if it was the right paragraph to build on that, to which Dr. Klaper said it was an example, not the point. Dr. Waters mentioned the language about understanding complex systems beyond mice and rats, and asking for better indicator species for ecosystem health. She asked if they wanted to move these ideas to the species section of the report. Dr. Klaper agreed, as it reflects earlier discussion, but should have a slightly different focus and should propose certain actions. Dr. Waters argued the program should decide how they will address that, which Dr. Klaper agreed with.

Dr. Waters then discussed the report section on lessons learned from ToxCast over the last six years. When the ToxCast program was launched, the high-throughput testing technology and computational chemistry approaches were already fairly mainstream, and yet still in the implementation of those capabilities, there were important shifts that had to be made along the way to move from a goal of predicting biological activities to prioritizing chemicals for Tier 2 testing. Looking forward to the microphysiological systems and computational biology approaches that are being employed in the complex systems program, they are really an order of magnitude more complicated than what they started with for ToxCast because they are rapidly emerging disciplines and moving targets. They asked the question of what can be learned from the history of the chemical evaluation program that can really ensure the success of the complex systems program. Furthermore, they questioned if they could look for ways to tap into existing resources for computational biology and other systems programs that exist out there that they might draw from.

Dr. Weisel said they heard that exposure and toxicology are an integral part of CSS, but asked what else did they miss in the analysis. Dr. Waters commented they left out the information and discussion on dosimetry and margins of exposure. Dr. Bahadori wanted them to remember CSS is a biological-based organization. Dr. Weisel pointed out they were in charge of ExpoCast. Dr. Bahadori replied they had ExpoCast, lifecycle modeling, and pharmokinetics, and the real question was what exposure components do they not have. Dr. Weisel asked if that was talked about in this section, and Dr. Waters replied they had not gotten to the life cycle section yet, but Dr. Weisel still wanted a sentence or two of understanding about exposures added to the section. Dr. Bahadori pointed to the project they had talked about, to which Dr. Weisel defended himself by saying he was not arguing with her and mentioned he was only talking about what is shown there. Dr. Stevens asked if he was referring to real world exposure and where they are measured. Dr. Weisel added there is data available to help influence the decision, and there needs to be an understanding of what exposures come together. Dr. Stevens argued they had purposely stayed toward the focus of the high throughput systems to move from concentration-based activity measurements in vitro to their current efforts to predict what they believe will be exposure based

biological activity. He believed taking real-world exposure data and working backwards is important, but that is should not be inserted in this section. Dr. Bahadori maintained they are doing it, and for example, they are reformulating consumer products to examine what exposures look like. Dr. Stevens admitted, when they got to that complex area, they had bundled everything under the term pharmacokinetics. Dr. Weisel wanted them to look at multiple chemicals, and stated they should not look at things in broad classes or as a list of arbitrary chemicals, but instead examine the combination as what chemicals are most likely to be there together. Dr. Stevens remarked it sounded like a mixtures issue more than a complex systems or chemical evaluations issue. Dr. Weisel insisted complex systems include mixtures. The group decided to add that point in the chemical evaluation section. Dr. Bahadori said complex mixtures are in both the AOP and chemical evaluation projects, and Dr. Weisel wanted this to be included. Dr. Bahadori differentiated between the environmental side and human side of CSS. The effect based monitoring poster would be an example of the environmental side, while the human side would include getting a handle on the actual exposures. Dr. Klaper thought there should be a good link between writing both sections, and Dr. Bahadori insisted parts be repeated.

Dr. Klaper brought up they had not even tackled part B yet, which where a lot of the modeling discussion was placed. Dr. McPartland asked if they were suggesting using mixtures to elucidate AOPs, to which Dr. Weisel responded in the negative. Dr. Stevens stated AOPs are physiologically based. Dr. Weisel thought what they were doing was looking at an AOP in a chemical sense. Dr. Waters maintained the AOP starts with the initiating event, and then goes forward. Dr. Johnson remarked in many cases what ends up there will be a mixture, but that it is not a mixture to start with. Dr. Bahadori thought it was a strong point to include, and also to put emphasis on co-occurring mixtures, which is something they want to do more of. Dr. Johnson added it also influenced the whole concept of biology, and Dr. Bahadori asked to also add it to that section. Dr. Waters said if anything else was missing, they would go back through the notes and pull the rest in. Dr. Somasundaran asked who would present charge question 4b, to which Dr. Klaper remarked they had not gotten to 4b and were still working on it.

Dr. Weisel started the discussion for charge question 6, saying it was a lot simpler to answer than the others, and their group had a near final draft. He listed the series of strengths. The first strength is that HHRA is adapting and propagating a much more open and transparent approach to efficient use of technology tools for conducting and reviewing risk analysis. They are bringing in information scientists to develop HERO is a brilliant resource that should help to integrate necessary literature reviews and in increase transparency for work products. Expo-Box houses many tools from the simplest to the more complex and has multiple different search capabilities with the potential for characterizing site specific exposures. BMDs provide an on-line framework for risk estimate that provide a comparison for different approaches. The second strength is that HHRA has appropriately linked information from CSS for establishing rapid toxicological information for novel and emerging chemicals. The third strength is HHRA is using system tools to identify new data and identify resources and expertise to develop risk evaluation for emergency response in collaboration with the needs with their regional partners. Emergency responses have included the West Virginia spill in of MCHM (methylcyclohexanemethanol) into the drinking water and the waste spill into recreational waters near the Gold King mine. Dr. Beamer clarified the Gold King mine area is designated as recreational water, and not drinking water, although there are Native American tribes who drink the water.

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Dr. Vandenberg made a comment about in house computational capabilities. Dr. Solomon asked for clarification if he meant using new data. Dr. Vandenberg replied this capability arose from previous BOSC review where there was an encouragement to increase capacity to respond to urgent needs, reflected in Project 5. It is not really about computational tools as much as capacity to tap into expertise. It is not computation as much as systems within an organization to identify and tap into expertise quickly. Dr. Solomon said the team was wrestling with framing charge question 6 around new data and computational tools and this issue seemed important to highlight. The issue might belong under charge question 2 or 3 instead, if it is not using new data and tools. They had thought HHRA was using new data for MCHM. Dr. Vandenberg replied they did and they had brought new data to bear in a lot of ways, but in response to a previous BOSC review, which is better answered under charge questions 2 and 3.

Dr. Weisel then listed the challenges they had written out. The program is heavily dependent upon IT and personnel resources, in particular to conduct the open reviews of the risk assessment. There is a need to have sufficient face to face and consultations with the regional scientists for training and utilization of the new tools. Furthermore, compiling older literature into the HERO database is time consuming. The second challenge is determining how long and at what level HHRA should support new risk assessment tools as they are adapted by the regional partners and their applications are shown to be valid. This should consider transferring knowledge to and training regional scientists and engaging the public in risk assessment. Points were made by the subcommittee about the differences between the program and the regional offices, and the technological support given to the regional offices versus the program offices. The third major challenge is that acute exposure evaluation using real-time sensor data is both an opportunity and challenge. Sensors can provide spatial and temporal concentration, they require additional levels of quality assurance in the field, and they generate large amounts of data requiring higher levels of expertise to interpret. They commended HHRA for addressing applying genetic and epigenetic data to inform susceptibility in cumulative risk assessment methods. Developing a framework for their incorporation and transmitting those approaches to a regional level will be a challenge but if successful will improve chemical risk assessment.

Dr. Weisel then listed the areas for improvement. They suggested an online guidance document for using Expo-Box be developed that considers the different levels of expertise of the intended users. Searches that bring up lists of websites should provide insight on the capability and inputs needed for deploying them. Furthermore, they need to provide a curation of the outputs to facilitate comparison and selection of result for specific applications. The second area of improvement was including non-chemical stressors as a one of the components of cumulative risk assessment as part of the cost benefit analysis, such as economic factors, environmental justice, stress, noise, and community concerns. The last area for improvement was augmenting the confidence the regions have with predicted risks from computational methods though combined effort of CSS and HHRA through necessary training and collaborations. This should continue and expand listening to the needs of the regional scientists which will vary across locales. Lastly, Dr. Weisel read off their list of recommendations. HHRA should develop approaches for acute and not just chronic risk assessment. These approaches may be well suited to new data streams. HHRA should better connect with scientists in the regional offices and NIEHS Superfund Centers to leverage the new tools in risk assessment to be relevant to specific sites and transmit information to the public. Lastly, HHRA should use the CSS rapid

toxicological and exposure tools to develop risk numbers for tentatively identified compounds in the environment. Dr. Vandenberg asserted that regions and programs have a lot of common ground.

Dr. Somasundaran moved the discussion to the whole document. Dr. Johnson asked, from an EPA side, what they thought was missing from the discussion. Dr. Bahadori remarked they wanted feedback on translation and interactions, which they received. She appreciated their remarks on science ideas, emphasis on exposure, and early adopters. She said any more ideas they can give CSS on actual pieces of science that are ready for early adopters would be useful. Dr. Vandenberg said he was impressed with their grasp of the overload of the information, but one thing they had missed was reflection that risk assessment is not a monolith and context matters. Dr. Beamer asked where they could fit these comments, and Dr. Solomon suggested they capture it under question six, especially the part about different approaches to risk assessment that can be used. Dr. Vandenberg asked them to use the word screening instead of assessment, as the process is not quite an assessment. Dr. Solomon stated NRC's recommendation of tailoring risk assessment to the decision context, and that in HHRA's efforts to embrace new data streams, they are seeing them do exactly that. They should bridge CSS data into assessments.

Dr. McPartland asked for the phrase "chemical evaluation activities" to be added. Dr. Bahadori said they called them safety evaluations. Dr. Weisel and Dr. Vandenberg talked about the use of the word screening, which has some specific meanings, and decided it was appropriate to use. Dr. Solomon wanted the word "nimble" included, as both programs are nimble in redirecting resources and responding. She asked if they should mention it under question one. Dr. Bahadori said the word would be a good way to express that the matrix format is working, as she can move resources between six labs and centers seamlessly, which was one of the goals of the reorganization. Dr. Stevens said the word nimble can also be used to refer to the support of regional needs, as he found it impressive the ways regions have responded. Dr. Johnson wanted to stress the importance of the organizations listening carefully to various groups. Dr. Somasundaran asked if understanding mechanisms was not part of the CSS mission, which Dr. Bahadori replied it was, as it was about 80% of their work. AOPs would be impossible without understanding the mechanisms.

Dr. Stevens had a special request. Since the BOSC subcommittee group will be together for three years, he was wondering if, because they are all brand new and have a several year time horizon, they should think about what to do in the future based on this meeting. He was unbelievably impressed with the way the programs were presented and sat for hours and answered questions articulately. He heard from some of the scientists about the larger conceptual framework, and there were occasions where they seemed cognizant, but not laser-beam focused. He suggested the organizations hear from some of the scientists on the matter and ask them what they see as the overarching deliverables. It would allow the BOSC to gauge whether they are fully integrated with the organization vision and if the vision is translating down to the individual program elements. Dr. Hubal suggested they deliver what Dr. Stevens would like to see with the next set of recommendations. The room agrees that it would be helpful to see as a recommendation of what they would like to see and review next. Dr. Stevens asked for comments from other

members for when to next discuss, Dr. Bahadori says no sooner than a year. Dr. Bahadori believe, in this initial stage, more frequent meetings would give them fodder, as they are toying with taking ecomodeling out of the life cycle area and putting it in complex systems. The group, for future meetings, should think if this reorganization would be a useful recommendation.

Dr. Johnson commented on the importance of face-to-face, even virtual, meetings and wanted future meetings to sit down with the people involved in order to go more in depth, get a greater understanding, and provide commentary. Dr. Klaper asked if they would be informed when the CSS scientists do webinars. Dr. Bahadori said they could look into it. Dr. Johnson said the discussion would not need to be webinar format, just not too PowerPoint based. There could be discussions with preliminary information sent out and then the members could discuss to really get an understanding of the programs in depth. Dr. Stevens loved the interaction with scientists at posters, but believed what would be more valuable would be meeting project leads to weigh the CSS vision against the feedback they are giving them. Dr. Bahadori replied the program is led by six laboratories and centers. Dr. Beamer recommended finding a better way to divide and conquer in the future, as they did not necessarily need to see everything. Dr. Bahadori responded they would have three additional members the next meeting, which should make it easier.

Wrap Up and Adjourn
Dr. Ponisseril Somasundaran & Dr. Gina Solomon

Dr. Somasundaran thanked the subcommittee for all of their hard work. Ms. Fleming added that she was thankful for them for coming and said they all did a wonderful job and worked hard. She said she would continue to follow up with future details and timeline checkpoints.

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Appendix A: Agenda

United States Environmental Protection Agency
Board of Scientific Counselors (BOSC) Subcommittee for
Chemical Safety for Sustainability (CSS) /Human Health Risk Assessment (HHRA)
Meeting Agenda – October 6-8, 2015
EPA Campus, Research Triangle Park, North Carolina; Room C-112

TIME	TOPIC	PRESENTER
Tuesday, October 6, 2015		
8:00 – 8:30	***Registration***	
8:30 – 8:45	Welcome, Introduction, and Opening Remarks	Ponisseril Somasundaran, Chair; Gina Solomon, Vice Chair
8:45 - 9:00	DFO Welcome and FACA Rules	Megan Fleming
9:00 – 9:15	Overview of Agenda, Structure of Joint CSS-HHRA Programmatic Review, and Discussion of Materials Provided	Tina Bahadori, CSS NPD John Vandenberg, HHRA NPD
9:15 – 9:45	Review and Assignment of Charge Questions	Ponisseril Somasundaran Gina Solomon
9:45 – 10:00	Break	
	CSS & HHRA Program Overviews	
10:00 – 11:30	CSS Program Purpose and Design (General Question 1) - EPA Overview - Subcommittee Discussion	Tina Bahadori Subcommittee
11:30 - 11:50	HHRA Program Purpose and Design (General Question 1) - EPA Overview - Subcommittee Discussion	John Vandenberg Subcommittee
11:50 – 12:30	***Lunch***	
12:30 – 2:00	Poster Session Building B Atrium	CSS and HHRA Project Leads

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	CSS Program	
2:00 – 3:30	Subcommittee Discussion of CSS Scope and Implementation of Research (General Questions 2 – 3, and CSS-specific Question 4) - Chemical Evaluation, CSS - Lifecycle Analytics, CSS - Complex Systems, CSS	Subcommittee Tina Bahadori
3:30 – 3:45	***Break***	
3:45 – 5:00	Subcommittee discussion of CSS Fit-For-Purpose Translation and Knowledge Delivery (CSS-specific Question 5) - Translation and Delivery, CSS	Subcommittee Tina Bahadori
5:00 – 5:30	***Subcommittee Wrap-up and Adjourn***	Ponisseril Somasundaran Gina Solomon
Wednesday, October 7, 2015		
8:30 – 10:30	CSS Genius Bar and Lab Tours Room C-113	CSS Project Leads
10:30 – 11:30	Poster Session Building B Atrium	CSS and HHRA Project Leads
11:30 – 12:30	Subcommittee discussion of CSS program EPA response to Subcommittee questions	Subcommittee Tina Bahadori
12:30 – 1:00	***Lunch***	
	HHRA Program	
1:00 - 1:50	HHRA Software Showcase Building B Room B-249	HHRA Project Leads
1:50 – 2:30	HHRA Projects #5 – 9 (General Questions 2 – 3 and HHRA-specific Question 6) - Site-specific Support and Emergency Response, HHRA - Cumulative Risk Assessment, HHRA - Advancing Hazard Characterization and Dose-response methods, HHRA - Applying Emerging Science, HHRA - Risk Assessment Support and Training, HHRA	Subcommittee John Vandenberg

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2:30 – 3:30	Subcommittee discussion of HHRA program EPA response to Subcommittee questions	Subcommittee John Vandenberg
3:30 – 3:45	***Break***	
	EPA Program and Regional Offices	
3:45 – 5:15	Program and Regional Office Perspectives on CSS and HHRA Programs (General Question 3)	TBD
5:15 – 5:30	Public comments (if any)	
5:30	***Wrap Up and Adjourn***	
Thursday, October 8, 2015		
8:30-9:30	Subcommittee group discussion of preliminary findings and recommendations	Subcommittee
9:30-12:00	Subcommittee breakout group by 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

Appendix B: Participants

BOSC CSS Subcommittee Members:

Ponisseril Somasundaran, *Chair*
Gina Solomon, *Vice Chair*
Paloma Beamer
Chris Gennings*
Dale Johnson
Rebecca Klaper
Kyle Kolaja*
Jerzy Leszczynski
Jennifer McPartland
James Stevens
Donna Vorhees
Katrina Waters
Clifford Weisel
Mark Weisner*

* Unable to attend

EPA Designated Federal Officer (DFO): Megan Fleming, *Office of Science Policy, ORD*

EPA Presenters:

Tina Bahadori, *Office of Research and Development, National Program Director for the CSS Research Program*
John Vandenberg, *Office of Research and Development, National Program Director for the HHRA Research Program*
Dan Axelrad*, *Office of Pesticides*
David Dix*, *Office of Chemical Safety and Pollution Prevention*
Bruce Duncan*, *Office of Research and Development, Region 10*
Robert Hillger, *Office of Research and Development, Region 1*
Bart Hoskins, *Office of Research and Development, Region 1*
Bryan Hubbell, *Office of Air and Radiation*
Kristen Keteles, *Office of Research and Development, Region 8*
Ron Landy, *Office of Research and Development, Region 3*
Jeff Morris*, *Office of Chemical Safety and Pollution Prevention*
Kathleen Raffaele, *Office of Solid Waste and Emergency Response*
Santhini Ramasamy, *Office of Water*

* Remote Participation

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Other EPA Attendees:

Barbara Abbott
Nicholas Anastas
James Avery
Christina Baghdikian
Jane Bare
Susanna Blair
Dermont Bouchard
William Boyes
David Bussard
Rory Connolly
John Cowden
Kevin Crofton
Allen Davis
Kathie Dionisio
Kevin Dreher
Ingrid Druwe
Steven Dutton
Stephen Edwards
Peter Egeghy
Drew Ekman
Matthew Etterson
Susan Euling
Lynn Flowers
Jill Franzosa
Annette Gatchett
Jeff Gift
Andrew Gillespie
Annette Guiseppi-Elie
Maureen Gwinn
Intaek Hahn
Wendy Heiger-Bernays
Daniel Hicks
Ron Hines
Andrew Hotchkiss
Keith Houck
Elaine Hubal
Annie Jarabek
Maureen Johnson
Ryan Jones
Robert Kavlock
John Kenneke
Barbara Klieforth
Thomas Knudsen
Andrew Kraft
Carlie LaLone
Jason Lambert
Meredith Lassiter
Janice Lee
Yu-Sheng Lin
Monica Linnenbrink
Michael Loughran
Todd Martin
Connie Meacham
Viktor Morozov
Holly Mortensen
Ginger Moser
William Mundy
Meghann Niesen
Bridget O'Brien
Paul Penn
Paul Price
Tom Purucker
Glenn Rice
Jennifer Richmond-Bryant
Kim Rogers
Kathryn Saterson
Paul Schlosser
Deborah Segal
Imran Shah
Bob Sonawane
Richard M. Spencer
Caroline Stevens
Kate Sullivan
Tamara Tal
Cecilia Tan
Kent Thomas
Russell Thomas
Lila Thornton
Joseph Tietge
Natalia VanDuyn
Katrina Varner
Dan Villeneuve
Sury Vulimiri
John Wambaugh
George Woodall
Erin Yost
Douglas Young
Richard Zepp
Robert Zucker
Benjamin Zukowski

Other Participants:

Inigo Montoya
Maureen Pittman
Edgar Winter

Contractor Support:

Courtney Skuce, ICF International
Canden Byrd, ICF International
Nicole Vetter, ICF International

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Appendix C: Charge Questions

General Board of Scientific Counselors Questions

Charge Question 1: Given the research objectives articulated in the StRAP, are the topics and project areas planned and organized appropriately to make good progress on these objectives in the 2016-2019 time frame?

Charge Question 2: How effective are the approaches for involving the EPA partners in the problem formulation stage of research planning?

Charge Question 3: How well does the program respond to the needs of EPA partners (program office and regional)?

CSS and HHRA Subcommittee Questions

Charge Question 4: Please provide input on the scope and implementation for 2016-19 in the following topic areas:

a. Complex Systems Science
b. Lifecycle Analytics
c. Chemical Evaluation

Charge Question 5: Please provide input on opportunities and approaches for fit-for-purpose translation and knowledge delivery.

Charge Question 6: Please comment on the research dimensions of the HHRA program and, in particular, the proposed approaches for characterization of new data and computational methods to improve confidence and build capacity for their application in the context of risk assessment.