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

Chemical Safety for Sustainability (CSS) Subcommittee

Face-to-Face Meeting Minutes

November 16–18, 2016

Date and Time: November 16, 2016, 8:30 a.m. to 6:00 p.m.; November 17, 2016, 8:30 a.m. to 6:00 p.m.; November 18, 2016, 8:30 a.m. to 3:30 p.m.

Location: EPA Campus – 109 T.W. Alexander Drive, Research Triangle Park, NC

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.

Wednesday, November 16 3

Welcome, Introduction, and Opening Remarks 3

Designated Federal Officer (DFO) Welcome and FACA Rules 3

Opening Remarks 5

Overview of Agenda, Organization of the Meeting, Discussion of Materials, and Highlights 5

Chemical Evaluation, Translation and Knowledge Delivery, and Complex Systems Science Topic Areas Research Project Deep Dives 7

Adverse Outcome Pathway Discovery and Development 7

High-throughput Toxicology 12

Rapid Exposure and Dosimetry 14

Demonstration and Evaluation 18

Virtual Tissues 20

Subcommittee Discussion and Deliberation 23

CSS Poster Session and Genius Bars 23

Subcommittee Discussion of Charge Questions 23

Wrap-up and Adjourn 29

Thursday, November 17 30

Welcome and Review of Day 1 30

Overview of Day 2 30

Life Cycle Analytics Topic Area Research Project Deep Dive 31

Sustainable Chemistry 31

Life Cycle - Human Exposure Modeling 35
Emerging Materials 37
Ecological Modeling 38
Subcommittee Discussion and Deliberation 40
EPA Program and Regional Offices 42
Program and Regional Offices Perspectives on CSS 42
CSS Poster Session and Genius Bars 45
Concurrent Genius Bars (RapidTox, CPDat, Chemistry Dashboard) 45
Subcommittee Discussion and Deliberation 45
Public Comments 47
Subcommittee Wrap Up and Adjourn 47

Friday, November 18 48
Welcome and Review of Day 1 and 2 48
Human Health and Risk Assessment (HHRA) National Research Project Update 48
HHRA Update 48
Subcommittee Group Discussion of Preliminary Findings and Recommendations 51
Discussion of Outstanding Issues, Review of Draft Report, Review of Timeline and Assignment of Follow Up Activities 51
Wrap Up and Adjourn 54

Appendix A: Agenda A-1

Appendix B: Participants B-1

Wednesday, November 16

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

Welcome, Introduction, and Opening Remarks

Dr. Ponisseril Somasundaran, Chair; Dr. Gina Solomon, Vice-Chair

Dr. Gina Solomon, Vice-Chair of the U.S. Environmental Protection Agency (EPA) Board of Scientific Counselors (BOSC) Chemical Safety for Sustainability (CSS) subcommittee formerly opened the meeting. She welcomed the subcommittee members to the meeting.

Dr. Solomon stated that like the previous year's meeting, the subcommittee members would receive an intense amount of information over the next 3 days. She shared that one new member has been added to the subcommittee and one additional subcommittee member will join the meeting later. This subcommittee meeting is the last BOSC meeting of the year, so the subcommittee will have limited time to submit their report to the BOSC Executive Committee Chair by late December.

Dr. Solomon asked the subcommittee members to draft a paragraph with some ideas before the conclusion of the subcommittee meeting. These ideas will be compiled and sent to the BOSC Executive Committee Chair by mid-December. She acknowledged the uncertainties associated with the pending changes to the EPA administration. These changes might impact some of the advice provided by the subcommittee. From Dr. Solomon's perspective, EPA staff in the CSS program will strive to protect the environment, fulfill their mandates, and do the best science. The subcommittee's job is to help optimize their work and encourage the program to go forward in the best direction. That will not change no matter what is happening in Washington, DC. She encouraged the subcommittee to stay focused on the most useful science.

Each subcommittee member introduced themselves stating their name, credentials, affiliation, research background, and areas of work interests.

Designated Federal Officer (DFO) Welcome and FACA Rules

Ms. Megan Fleming, Designated Federal Official

Ms. Megan Fleming introduced her role as the subcommittee DFO, and explained the Federal Advisory Committee Act (FACA) guidelines relevant to the proceedings. The meeting would focus entirely on CSS with a brief update on the Human Health and Risk Assessment (HHRA) program on Friday, November 18. The goal was to deliver a report to the BOSC Executive Committee by late December in preparation for the January BOSC Executive Committee meeting.

She asked subcommittee members to remember:

- all BOSC activities must comply with FACA,
- group emails are potentially subject to FACA guidelines, and therefore she should be copied on all electronic communications among the group,

- drafts of reports and substantive comments can be emailed directly to the chair, vice-chair and should also have the DFO copied,
- all BOSC meetings must be open to the public,
- a member should notify her if they had any conflict-of-interest concerns,
- the subcommittee chair and vice-chair are responsible for running the meeting, according to the preprinted agenda and manage any necessary deviations from the agenda, and recognize audience members and other subcommittee members to speak,
- all records are maintained and open to the public,
- meetings are advertised in the Federal Register,
- meeting minutes will be made available to the public following the meeting,
- all members have had ethics training and ethics regulations have been followed, and
- subcommittee members do not have conversations with EPA members to request documents; they contact the DFO for any document requests.

Ms. Fleming stated that no requests for public comments had been received in advance of the meeting. If public comments are received, they will be read on Day 2 of the meeting and each comment will be limited to 3 minutes. Ms. Fleming certified for the record that everyone expected to be present for the meeting that morning was accounted for. Eleven subcommittee members were present. Dr. Mark Wiesner will join the meeting after lunch. Dr. Jerzy Leszczynski and Dr. Kyle Kolaja would not be able to attend the subcommittee meeting. She encouraged all participants to sign in at the registration desk.

While waiting for Dr. Bob Kavlock to dial in, Dr. Solomon mentioned that posters and new tools developed by CSS scientists would be on display in the afternoon of Day 1. She asked the subcommittee members to view posters related to their area of expertise, such as nanomaterials, ecotoxicity, and exposure science, among others. At the end of the day, the subcommittee members would have time to debrief and share their initial impressions of the posters and new tools.

Dr. Ponisseril Somasundaran read the charge questions aloud to the subcommittee. Dr. Solomon stated that the Science Advisory Board (SAB) provides guidance to the entire Agency. The BOSC provides guidance to the Office of Research and Development (ORD) and the subcommittee provides guidance specifically to the CSS program. There were only two charge questions, but there were also sub-questions that required their attention. The charge questions were broad and can be taken in whatever direction that the subcommittee saw most appropriate. They provide the subcommittee with latitude. Subcommittee members should consider if the information from the presentations, poster session, and genius bars were useful for the goal of providing a scientific foundation for EPA's mission of protecting human health and the environment. The subcommittee members should also consider if the information is relevant and if important areas of science are missing.

Opening Remarks
Dr. Bob Kavlock, ORD Deputy Assistant Administrator for Science

Dr. Kavlock joined via webinar and stated that he had planned to attend the meeting in person. Due to the presidential transition, he had to stay in Washington, DC, to await the announcement of the "landing team" that would receive briefings on the various aspects of the Agency's operations. He stated that the work that the team is doing is important because a strong science program that is vetted properly and reviewed closely is needed. He looked forward to the Executive Committee meeting in January when all reports of the BOSC subcommittees will be reviewed. The Toxic Substances Control Act (TSCA) reform bill was passed in the summer of 2015, and the Agency was gearing up for its implementation. CSS was instrumental in helping organize an international workshop in September of 2015 where regulators from around the world were asked to discuss their experiences with using alternative methods for accelerating the pace of risk assessment. Regulators were also asked about barriers to accessing some of the data in the regulatory process. Ten barriers were listed and an article was published in the *Bureau of National Affairs (BNA) News* about the workshop. Participants in the workshop were also asked to develop case studies that could be used to address these barriers. Eight case studies were proposed and the workshop participants would have a teleconference the following week to encourage cooperation from the international community. Because the chemical industry is global, the changes in processes require a global solution. CSS played a key role in organizing the workshop and promoting the case studies. Dr. Kavlock stated that he appreciated everyone's time and effort and looked forward to constructive criticism as they go forward. He then turned the meeting over to Dr. Tina Bahadori.

Overview of Agenda, Organization of the Meeting, Discussion of Materials, and Highlights
Dr. Tina Bahadori, CSS National Program Director

Dr. Bahadori explained that the current meeting was a bit different from the previous year due to feedback received from the subcommittee members. Program and regional partners were invited to join this meeting based on this feedback. These partners will participate in a panel session on Thursday, November 17. She introduced the following regional scientists: Marie O'Shea (Region 2), Wendy O'Brien (Region 8), Bruce Duncan (Region 10), and Carole Braverman (Region 5; by phone/webinar). She also introduced partners from the program offices: Kathleen Raffaele (Office of Land and Emergency Management), Eva Wong (Office of Pollution Prevention and Toxics), Daniel Chang (National Exposure Research Laboratory [NERL]), Tala Henry (Office of Chemical Safety and Pollution Prevention (OCSPP) Office of Pollution Prevention and Toxics), Betsy Behl (Office of Water), Stan Barone (Office of Science Coordination and Policy), Seema Schappelle (Division Director of the Office of Science Coordination and Policy), and John Vandenberg (National Center for Environmental Assessment [NCEA]) Dr. Vandenberg will present on Friday morning, November 18.

Dr. Bahadori also introduced her team which had gotten smaller since the previous year. She shared that Elaine Hubel was on detail to the National Health and Environmental Effects Research Laboratory (NHEERL). Other team members included John Cowden, Mike Loughran, Jill Franzosa, Susanna Blair, Ben Zukowski (student contractor), Rachel Matney, John Kenneke,

Santhini Ramasamy, Joseph Tietge, Doug Young, Monica Linnenbrink, Dayna Gibbons, and Kelsey Maloney. The project leads will introduce themselves during their presentations.

Dr. Bahadori summarized the agenda. The CSS Program has four research topic areas. There is integration within and across the projects and topic areas. Day 1 of the meeting is focused on chemical evaluation, complex system science, and translation and knowledge delivery. On Day 2 of the meeting, the focus would be on life cycle analytics (LCA), sustainable chemistry, emerging materials, life cycle human exposure modeling, and ecological modeling. As subcommittee members considered splitting their expertise, they would notice that the meeting days were clustered around biology and then technology with ecological modeling discussed across both areas.

The group spent time discussing charge questions earlier in the day. With respect to consideration of resource limitations, the subcommittee should consider if there were any significant scientific gaps within the established domain. The subcommittee should also consider if there are obvious topics or projects that CSS is not doing and/or not aware of. This is more of a check on the soundness of the science and the integration based on feedback from the subcommittee in the previous year's report. Subcommittee members were given a binder, and Dr. Bahadori reviewed the contents so that all subcommittee members could become familiar with the materials. The binder included a meeting agenda; the roster and biographies of subcommittee members; the CSS team roster; and agenda narrative and charge questions; the BOSC Poster and Genius Bar guide; the CSS topic project lead guide; a list of CSS fiscal year (FY) 2017 proposed products; a map of EPA's Research Triangle Park (RTP) campus; presentation slides; and poster handouts. She also pointed out that the posters were located in the atrium and the room location for each Genius Bar. Other materials provided to the subcommittee in advance included the FY16–19 Strategic Research Action Plan (StRAP); an overview of CSS; the HHRA FY16–19 StRAP; an overview of HHRA; and EPA's response to the BOSC 2016 review.

Another difference at the 2016 meeting was that members would hear presentations and posters directly from scientists, not just project leads. The presentations from the project leads would provide a high level panoramic view about their products. Day 1 would consist of five presentations in the morning session. After lunch, members would view the posters and visit the Genius Bar for the first half of the afternoon. Dr. Bahadori noted only posters 1 through 23 would be staffed on the first day and the rest of the posters would be staffed on the second day of the meeting. The first day of the meeting would be more focused on ecological science. The subcommittee would then return to the conference room for deliberation and discussion. On day 2, the focus would be on LCA projects and a panel of program and regional partners would convene. Dr. Braverman from Region 5 would give a presentation on the collaboration that CSS has in support of the Great Lakes project and the other panelists would give five minute perspective comments. There would be 45 minutes at the end of the day for questions and answers. Day 3 would include deliberation and a review of the HHRA program.

The CSS program resources budget was presented. The budget was still under a Continuing Resolution (CR) which would stay in effect until December and through March. The resources for the Science to Achieve Results (STAR) research program are also managed in that same

budget. It includes about $9 million for STAR grants. Because CSS is organized by topic, Dr. Bahadori presented a pie chart to show the percentage of the budget by topic. Complex Systems Sciences includes extramural resources so the funds go to the university partners. A separate pie chart illustrated the CSS budget by projects. She suggested the subcommittee members consider a review of accomplishments that have occurred since the last subcommittee meeting as they meet the scientists and view the posters. The emphasis on the adverse outcome pathway (AOP) framework as a guiding principle of the program was coming into fruition. It is being taken seriously and there is a lot of international collaboration built around AOPs. CSS would continue to support AOP research. CSS launched a large effort focused on training and outreach for federal partners and the international community. There has been a big emphasis on the integration of human and ecotoxicology with the expansion of the Ecotoxicology Knowledgebase (ECOTOX). There is momentum around expanding the repro-neuro-endocrine area and the endocrine space. The subcommittee members will see a presentation on the progress being made in the area of virtual tissues modeling (VTM). Exploratory efforts in cancer research are underway and several publications were released as a result of project work in that area. Assuming resources are available, researchers are also looking at types of cancer screening.

Dr. Bahadori stated the exposure-dose-response effort has exploded in terms of the level of integration. The focus on chemistry includes the selection of safer alternatives and the CompTox Chemistry Dashboard would be reviewed later. With respect to emerging materials, work is focused on nanomaterials and the development of a knowledge base. There is also an effort to build capacity in exploratory biotechnology. Stakeholder engagement and outreach efforts were re-doubled in Translation and Knowledge Delivery which included regions, states, the United States (U.S.) Food and Drug Administration (FDA), and the U.S. Consumer Product Safety Commission (CPSC) in the application of the tools. There was also exploratory work done in developing metrics of impact. Work was done in the application of data to risk-based evaluations. The Endocrine Disruptor Screening Program (EDSP) will continue to grow and evolve. Members would see applications of RapidTox and many case studies. Dr. Bahadori stated that she is excited to have a program that can be prepared to support the implementation of the new TSCA. She shared that Dr. Tala Henry and her division would participate in the subcommittee meeting and that members can hear from them and began to consider how the science could be helpful.

Chemical Evaluation, Translation and Knowledge Delivery, and Complex Systems Science Topic Areas Research Project Deep Dives

Adverse Outcome Pathway Discovery and Development

Dr. Dan Villeneuve

Dr. Dan Villeneuve gave an overview of the AOP Project. His co-lead on the project is Dr. Stephen Edwards. AOPs is a framework that helps one connect molecular initiating events where a chemical interacts with a molecule in the body of an organism causing a perturbation in its biology. If the perturbation is sufficiently severe, it can progress to an adverse outcome that is important within a risk assessment context. It impacts the survival, growth, and reproduction of

wildlife and human health. Dr. Villeneuve stated that these issues are managed and regulated. He showed a graphic representation of an AOP that was developed which linked thyroperoxidase (TPO) inhibition to impacts on cognitive functions in mammals. The TPO assay was developed through the high-throughput toxicity (HTT) testing program for chemicals. The AOP might link chemicals and their mode of action (MOA) to a potential hazard. Each of the items along the pathway are measureable biological changes that can track progression along the AOP. The arrows on the graphic represent what is known about the biology, structural, and functional relationship between the enzyme activity and the synthesis of thyroid hormones and how euthyroid thyroid hormones impact neurodevelopment. Dr. Villeneuve and his colleagues sought to understand how these relationships translate to an impact of cognitive function. Understanding the biology and empirical evidence from research studies that support this lies behind the overall graphical depiction and what is included in an AOP description. This understanding can be expanded to produce a network that shows not only impacts in mammals but also how those impacts can diverge. For example, impacts on serum thyroid hormone concentrations can impact amphibian metamorphosis and other changes in fish. It can also be expanded to look at other molecular initiating events. Modular descriptions can be built of these pathways to a broader systems or network of understanding. Overall, it guides the interest in AOPs and what they can potentially do for the Agency.

Dr. Villeneuve provided other examples of what AOPs can do for the Agency. First and foremost, Dr. Villeneuve stated they want to enhance the use of mechanistic data in regulatory decision-making and provide that bridge from mechanistic pathway perturbation data to the things they care about from a risk assessment perspective. Pathway descriptions are used to support a more hypothesis-driven approach to testing and relaying the potentials hazards and changes that can be measured that reflect progression towards those hazards. These are endpoints that can be targeted in testing. These endpoints also inform appropriate cross-species extrapolation and help focus testing on species, life-stages, and taxa of concern given a chemical's mechanism. They also aid a strategic knowledge-driven approach to evaluating complex mixtures. Organizing information in this framework helps to identify critical knowledge and evidence gaps that impede the application of these types of mechanistic data.

Dr. Villeneuve emphasized the importance of recognizing what AOPs cannot do. AOPs are not risk assessments and the focus is on the biology and what happens when biological systems are perturbed. Risk assessments require consideration of exposure in the equation and integration with the rapid exposure and dosimetry project. There is a task project working on the interface between absorption, distribution, metabolism, and excretion (ADME) exposure and AOPs. AOPs are not synonymous with HTT or pathway-based testing, but they help translate data from ToxCast and other programs as well as other sources of mechanistic data for risk assessment. AOPs are not computational models, but computational models can be aligned with key events for dynamic simulations of dose response time course behaviors where there is sufficient understanding of those key relationships. AOPs are not a panacea; they will not solve the problems of *in vitro/in vivo* extrapolation and they will not account for every potential environmental, genetic, and dietary variable that could influence or modulate some of these

responses. AOPs help the program take what they know from the available evidence, literature, and biological understanding and apply this information to decision making.

Dr. Villeneuve noted that the project scope is divided into four major areas: 1) develop scientifically sound AOP descriptions; this includes generating novel experimental data related to these pathways and organizing existing knowledge from the literature and other sources into the descriptions; 2) develop guidance, tools, and infrastructure to facilitate transfer of AOP knowledge. If the information is not made available to people that do the decision making then the AOP is not helpful; 3) test the AOP-based predictions to build confidence in the AOP knowledge. If they do not have confidence that the predictions can be made along these pathways then no one would use them; and 4) conduct various case studies to demonstrate application in different risk assessment contexts. Working with the program office regional partners, case studies are developed that relate to decision making. These partners need to be shown how AOP tools can aid in decision making.

There is a strong international presence working with the Organization for Economic Cooperation and Development (OECD) and the international community on development of guidance on AOPs. Training has taken place all over the world on application of the AOP framework, collaborative AOP development, and the use and structure of the knowledge base. The major effort has been the development of the AOP Wiki, the knowledge platform that acts as the single authoritative source for AOP descriptions.

The project team has contributed more than 70 different AOPs to the AOP Wiki. The wiki contains at least 43 pathways that are relevant to ToxCast assays. There are links through the iCSS dashboard to those descriptions in the AOP Wiki. There are at least 43 ToxCast assay targets which have AOPs. AOP development ranges from newly hypothesized AOPs to well established AOPs for which there is a lot of evidence and qualitative understanding. The major focus areas based on the expertise of the team are: vertebrate reproduction, thyroid axis disruption, hepatic steatosis, cancer and reactive toxicant-mediated target organ toxicity. In addition to the work of Dr. Villeneuve's project team, there is collaboration with external partners to expand the scope of AOP development. They are expanding into targets that are specific to ecotoxicology, endocrine systems, and impacts of epigenetics. The team is also looking at how they can use computational approaches to accelerate the process of AOP development. Different database sources and various computational approaches are used to find relationships between chemicals and pathway perturbations to disease. These pieces are being put together to help develop more AOPs.

Various tools have been developed to access the taxonomic relevance of different high-throughput testing assays and related AOPs. The SeqAPASS tool was demonstrated at the Genius Bar and was developed to look at conservation of protein targets across a broad range of species.

As AOPs and AOP networks are developed, the team uses application case studies to show how they can be applied in the decision making framework. An AOP network of antiandrogens has been developed to explain why certain chemicals might not be picked up in the current EDSP screening batteries of antiandrogens. This network is also used to provide quantitative predictors

of postnatal consequences of *in utero* exposure to antiandrogens to reduce or replace animal use as mandated in the 2016 TSCA laws.

The team has collaborated with the Office of Pesticide Programs (OPP) on an application case study related to developing an AOP network for the effect of insecticides on honey bees. The team wants to consider not only the effects of the chemicals and the potential mechanisms of action but also how other environmental variables enter in the equation. This would help build a broader AOP network to synthesize and organize an extensive body of literature on that topic.

The case studies with regions have been looking at the effects of pathway based tools and AOPs as it relates to environmental monitoring. As a part of that effort, there is a partnership with U.S. Geological Survey (USGS) to leverage their capability to collect water samples. By conducting analytical chemistry analysis, the team brought to bear tools that look at the pathway perturbations associated with those chemicals. They developed a tool to calculate exposure activity ratio which compares concentrations detected in environmental samples with the effect concentrations in ToxCast. This allows for the prioritization of chemicals based on their concentration and relative potency against different pathways.

These types of tools have been applied to various types of case studies. There is a strong partnership with the Great Lakes National Program Office in Region 5 to look at tributaries and other regions across the country. Sites have been identified with high levels of contamination and evidence of potential biological effects. At these sites, the team will target cases and conduct integrated application case studies with multiple federal partners. They will identify effects in resident organisms as well as caged fish and muscles placed at these sites. The team will look across the AOPs to see if there is evidence of the kinds of hazards that they might predict based on the pathway perturbations that samples from those sites caused. The different types of assays will be applied *in vivo* and *in vitro*.

In order to apply AOPs in risk assessment there must be a linkage to exposure. The project has a task that focuses specifically on ADME integration with the chemical agnostic AOP framework.

There has been work with the Office of Water as they revised the 1985 Guidelines for Deriving Numerical National Water Quality Criteria. Case studies are being done to find out how they can develop pathway tools and AOP frameworks to help that process. Projects are also in the works with Sustainable Tools and Water Resources to help support their process.

Now that there is a critical mass of AOPs developed in the knowledge base, they are moving towards the application of AOP networks and consideration of multiple chemicals and scenarios. Within these scenarios, individual chemicals impact multiple pathways and there is exposure to complex mixtures. They are considering how this AOP network can be used to understand and predict the hazards associated with those types of exposures. The goal of this project is to make various tools and data sets generated through the project accessible to the public and other user audiences. SeqAPASS and the AOP Wiki are currently accessible and other tools and databases are in development. Developing an information technology (IT) platform that will make the tools available and interoperable will help users apply this information.

Dr. Bahadori explained that she only quickly reviewed the key aspects of the project. The project team contributes to all of the areas recognized.

Discussion

Dr. Clifford Weisel asked if they had looked at how AOPs could change across aging of individuals. Dr. Bahadori explained that, in terms of age, life stage is considered. However, things like age, diet, genetic background have not been accounted for. Where those types of modulating factors are known and understood in the literature gets put into the AOP and is captured in the key event relationship.

Dr. James Stevens asked how an AOP-based prediction is tested. Dr. Bahadori provided an example of an AOP linking aromatase inhibition to reproductive dysfunction in fish. ToxCast was used to test the AOP to look at chemicals that showed hits on aromatase inhibition assays and used chemicals that had never been tested before. Those were taken into the laboratory and a quantitative AOP model was used to run simulations to identify dose ranges to test. When the chemical is tested, they look to see if it produced that pattern of effects predicted based on the AOP. They also determine if the outcome was seen and if the prediction was close.

Dr. Chris Gennings asked how AOPs could be integrated with epidemiology studies where there are prenatal exposures of multiple chemicals and health effects in children are later observed. He asked if the mother could be considered if effects are observed in children along with early life exposures. Dr. Bahadori stated it might be possible, but has not yet been considered. An epidemiologist is involved in this project and looks at AOP development with epidemiological evidence and potential exposures. The linking mechanism could be identified by back tracking. This case study has not been completed.

Dr. Dale Johnson asked Dr. Bahadori to explain how they determine the case studies and if they require a large database of information. Dr. Bahadori explained that case studies are identified through interaction with the program offices. They have a need for a process and see a use for the AOP framework to help them with a process. CSS performs outreach to explain their research efforts and identify areas of opportunity where research can inform decision making.

Dr. Katrina Waters asked if the assays are connected to ToxCast in such a way that they are contributing new assays for high-throughput screening or if the development happened within the project. Dr. Bahadori clarified that assay development happens within HTT and also with collaborators.

Dr. Jennifer McPartland asked if machine learning techniques had been applied to complete literature mining in the development of AOPs. Dr. Bahadori replied that data mining had been employed but that machine learning was not. Data are mined from existing annotation data and already structured information (not literature). There are a couple of publications on the methods. Literature mining is an area that they are exploring and there are early efforts focused on systematic review.

Dr. Gennings asked if human biomonitoring data are used to inform their work or if most data are environmental. Dr. Bahadori replied that mostly environmental data have been used, but these concepts could be equally applied to human biomonitoring data.

High-throughput Toxicology

Dr. Tim Shafer

Dr. Tim Shafer stated that the goals of high-throughput toxicology (HTT) include developing a framework for validation of the HTT assays, providing better coverage of key toxicity pathways and adverse outcomes that are not currently well covered by ToxCast, and expanding the classes of chemicals that can be screened. The latest technological approaches are incorporated into the screening.

There are three major tasks of HTT:

1. Provide guidance for evaluating technical performance and biological domains of HTT assays, and generating lists of reference chemicals so that assays can be properly evaluated,
2. Develop new medium- and high-throughput assays and development of models to cover important areas of biological space/priority adverse outcomes, and
3. Incorporate mechanisms of xenobiotic metabolism and testing challenging chemical classes into high-throughput test methods.

Dr. Tim Shafer reviewed the projects in each task area and the related posters.

Highlights for Task 1

Reference chemicals: The objective was to provide a basis for evaluating the performance of high-throughput assays. Regulators need to understand the fit-for-purpose. There needs to be a list of reference chemicals to properly evaluate assays as well as annotations which are important. Projects in the area include building a list of reference chemicals for EDSP models and building high-throughput methods to identify reference compounds for additional ToxCast assays. A recent publication from this work described the evaluation of the level of evidence for developmental neurotoxicity of approximately 400 chemical compounds. A list of 100 chemicals were found to cause neurotoxicity in mammals.[1]

Assay annotation: There is ongoing work to develop standardized descriptors for HTT assay characteristics, biological domains covered, and interpretation of data based on level of biological complexity of AOPs. OECD has published guidelines to the kind of information that should be provided when assays are developed and annotated. The approach was to mirror the information that OECD guidelines provided as much as possible. This was used to develop an annotation schema for the ToxCast assays that will be uploaded to the CSS dashboards. When users are looking for ToxCast assays, they will be able to use the dashboard to get information about the species that the assay was conducted in, the measured endpoints, and how these

[1] Mundy, W.R., et al. Expanding the test set: Chemicals with potential to disrupt mammalian brain development. *Neurotoxicol. Teratol*. 52:25-35, 2015

endpoints were measured. The information will help scientists understand and interpret the data coming from those assays.

Highlights for Task 2

Assay development: The project objective is to develop novel assays to cover important biological spaces/high priority adverse outcomes. The major focuses are the thyroid and developmental neurotoxicity. The role in HHT is to develop new assays to cover critical key events in the thyroid AOP.

The progress made in developing assays for TPO, NIS inhibition, and deiodinase were briefly reviewed.

- TPO assay developed and 1,900 compounds screened in concentration-response; 1,100 compounds are available in ToxCast; there are two peer-reviewed manuscripts,
- NIS assay developed and ToxCast Ph1 and Ph2 compound screening in progress; the manuscript is in revision, and
- Dio-1 assay developed and ToxCast Phase 1 screening completed; Ph2 and e1K in progress; assays for Dio-2,3 have been developed.

Developmental neurotoxicity: There are few AOPs available for developmental neurotoxicity. Key processes in the development of the nervous system can be studied to develop these assays. The focus in recent years had been on assay development and evaluation. There were six assays developed that cover structure, function, and behavior. Fourteen peer-reviewed manuscripts and two book chapters came out of the work with those assays. One of the neurophysiology assays developed is unique in that multiple measurements can be made over time as networks develop. There are numerous assays that have been developed and there is a need to provide unsupervised ranking of chemicals across all of the assays taking into consideration the data generated across these assays. The development of unbiased ways of ranking is ongoing. In relation to the AOPs project, there are only two AOPs in the wiki database related to developmental neurotoxicity, so there is a need to develop proposed AOPs for developmental neurotoxicity. Currently, the developmental neurotoxicity assays are aligned with key events in AOP development. As more chemicals are screened through these assays, it will contribute to the AOP discovery related to developmental neurotoxicity.

Highlights for Task 3

In vitro assay improvements: This involves improving the ability to test chemicals that are difficult to handle. It would involve *in vitro* assays as well as incorporating biotransformation. A manifold system had been developed where volatile compounds can be exposed to systems that need to be fully characterized prior to their use to understand their advantages and limitations. It will be used to study the effects of chemicals on global transcriptomics. In terms of incorporating metabolism and biotransformation in the *in vitro* assays, the two strategies used included "extracellular" and "intracellular." There has been more emphasis on the extracellular approach because it is a potable way of moving the metabolizing components in to different cell models. Another approach that the team is taking is more mechanistic because it provides information about how different chemicals are metabolized. One of ways that the team wants to move

forward is to develop a comprehensive transcriptomic screening method. It is low cost and can be done in multiple cell models using ribonucleic acid (RNA) sequencing. It would facilitate in identifying which type of toxicity to focus on.

Discussion

Dr. Klaper asked if variations were observed across chemicals from different manufacturers. Dr. Shafer answered that their reference lists are focused on validation and evaluation rather than the source of the chemical.

Dr. Gennings asked if they have put chemicals together in a mixture to see if they might anticipate that what happens actually happens. Dr. Gennings asked what the group is doing in terms of using an approach targeted to a known exposure to a specific chemical combination. Dr. Shafer explained the chemical reference list included individual chemicals because the idea is validation or evaluation of different assays. For developmental neurotoxicity, they have not gotten to the point where they have begun running mixtures. Dr. Gennings asked if they anticipate that with the results associated with a single chemical would be similar for a mixture. Dr. Gennings asked if risks are under or over estimated. Dr. Shafer responded that they were looking at the relationship with the toxicity of the total mixture. There is no regulatory context for mixtures.

Dr. Waters asked if they were disseminating assay performance information with the assay annotation. She also asked if they were using that information to start assay attrition and if assays would be removed from their pipeline that they are no longer running or generating data from. Dr. Shafer confirmed that this approach is being used. The goal is to use the reference chemical lists to evaluate assay performance. The dashboard would have the performance data so everyone could looks at the results and use their judgement on assay utility. With respect to attrition, assays with high variability are no longer used.

Dr. Johnson asked if they are identifying metabolites that were being generated. Dr. Shafer answered that in the extracellular project, they are taking some gold standard compounds and making sure the expected metabolites are generated. He was unsure if this approach will be used in every case because it would require a significant amount of resources.

Rapid Exposure and Dosimetry

Dr. John Wambaugh

Dr. John Wambaugh noted that Dr. Kristin Isaacs is also part of the project. He stated that this is presentation provides a brief overview of their current work. There were four posters that were presented on this topic at the meeting. One primary example of where their research in rapid exposure and dosimetry were used was in support of the Office of Science Coordination and Policy (OSCP)'s EDSP to result in a high-throughput risk-based prioritization. He challenged the group to think about the work they saw in the HTT presentation identifying hazard in a high-throughput manner. Dr. Wambaugh stated that rapid exposure and dosimetry are needed within the program. For instance, if a user had a chemical that was interesting and one micromolar *in vitro*, the rapid exposure and dosimetry program provided the pharmacokinetic tools to translate

that into a human equivalent dose (milligrams [mg] per kilogram [kg] per day). This represents an exposure rate. Similarly, the user needs to generate a high-throughput exposure number. For any arbitrary chemical, with the exception of pesticides, it is difficult to get an arbitrary exposure rate. Dr. Wambaugh described a graph as having ToxCast-derived receptor bioactivity converted to mg/kg/day and exposure. He noted there are uncertain numbers coming out of their initial models.

Dr. Wambaugh first discussed rapid dosimetry, which included HTT and demonstration and evaluation. Their premier product result was their High-throughput Toxicokinetics (HTTK) R package for reverse dosimetry and physiologically based pharmacokinetic (PBPK) modeling (human, monkey, mouse, rat, and dog). It is available to all users for download and has all of their data, models, and documentation on how to develop the figures in their papers. The current version of the package is 1.4 and it includes 543 chemicals. Additional chemicals are being added and a "how-to" manuscript was published in the Journal of Statistical Software (Pearce *et al.*). It is an ongoing process, but their data and models are public. One of the new versions allows predictions of parameters based on actual National Health and Nutrition Examination Survey (NHANES) biometrics (e.g., different age populations throughout the United States). This is used in their ExpoCast project. Demographic-specific predictions of exposure for their HTTK package and demographic-specific predictions of toxicokinetics are also available. Dr. Wambaugh noted that within his slides, if the subject is red they are high risk, and if they are blue they are low risk. For example, women of reproductive age are at higher risk for exposure to parabens. A high-throughput human gestational model is also in development which covers human gestation from week 13 through delivery. The user is able to simulate gestational exposure for all of the chemicals. Dr. Wambaugh explained they do not trust their models. There are 2,000 chemicals they really want a PBPK model for. All of the PBPK models they have are chemical-specific, but calibrated *in vitro*.

Next, Dr. Wambaugh discussed rapid exposure. A careful systematic analysis of the NHANES biomonitoring data for the chemicals indicated in the American population has been conducted. A clear signal that the exposure pathway drives exposure was observed. Chemicals that were in products in homes (particularly with consumer use) were high in most Americans. Dr. Isaacs and her team developed the High-throughput Stochastic Human Exposure Dose Simulation Model (SHEDS-HT) which allows the simulation of rapid human exposure in the indoor environment. The model needs to be parameterized, so a series of databases have been built to display what chemicals are in products (e.g., the Functional Use [FUse] Dataset that has over 14,000 chemicals and over 200 functions). The FUse Dataset allows for modeling of function in terms of chemical properties or structures. Unfortunately, the FUse Dataset does not cover all of the chemicals of interest, so machine learning tools have been used to fill in the gaps. The database serves as a training set. Dr. Wambaugh explained that the structure of a chemical can be used to predict functional use and weight fraction for thousands of chemicals. The database can be used to answer questions such as "Does the chemical look like a perfume?" or "Does the chemical look like a plasticizer?"

Dr. Wambaugh noted that in addition to modeling, the group seeks to obtain new data. They are particularly interested in suspect screening and non-targeted analysis mass spectrometry. Non-targeted analytical chemistry is where a user studies the static and pays attention to as many signals as they can in that sample. There is an ongoing ExpoCast contract focused on consumer product scanning and blood sample monitoring. It will be used to put ToxCast chemicals *in vitro* into hepatocytes. The compounds formed from that metabolism will be observed. Dr. Wambaugh shared that significant capability with non-targeted analysis mass spectrometry (e.g., published on analysis of house dust from American homes) is available in-house. Researchers can identify many of the prevalent chemicals, but only 2 percent of the chemicals in the house dust could be identified at the time of the meeting. EPA is coordinating an international collaboration on non-targeted screening workflows used by leading academic and government groups using known chemical mixtures (ToxCast) and standardized environmental/biological samples (led by Dr. Jon Sobus and Dr. Elin Ulrich).

One result was a consumer product scan among 100 test objects from a United States retailer and it found that 3,803 need chemical signatures, 1,506 were associated with a tentative identification, and 126 had confirmed identities. These were all consumer products. Only 200 of the 1,600 chemicals were previously in the database of consumer product chemicals. That is exposure surveillance. With non-targeted analytical chemistry, many of the tools are identified via mass spectrometry or purely by mass. Dr. Wambaugh stated they are expanding their libraries using ToxCast chemicals to prioritize and enable greater numbers and better accuracy of confirmed chemicals. They will continue to provide better exposure forecasts and pharmacokinetic models. He mentioned everyone in their group is involved in the high-throughput exposure "forensics" and they predict in a forward mode. If someone is curious about a sample in water that makes it taste like licorice, they can take those samples, look at its molecular features, and consult their database. The database constructed by Dr. Tony Williams and the rest of the group contains 750,000 known structures. This database can be used to help predict the chemical of interest. This is exposure forensics: how do you understand where a chemical came from and how did it come to be in a sample?

Dr. Wambaugh explained the graph displayed frequent item set mining used to identify combinations of NHANES group B chemicals occurring in individuals at a concentration greater than the population median. He stated the numbers on the side of the graph were fractions of the United States population in which the mixture occurred. For example, if they are looking to test a mixture, there is a mixture that affects 43 percent of people in the United States. If one can predict how a chemical can be used and ToxCast and Tox21 tested 8,000 chemicals, prediction models can be run for all of those chemicals. He noted they are also well integrated in all the other topics/projects.

Discussion

Dr. Johnson asked about taking models and integrating them into additional models. Dr. Wambaugh responded that there were two ways to integrate models. A "super-model" can be built that integrates both models or they could obtain data. One of the reasons for conducting non-targeted analysis is to get the data to predict model performance.

Dr. Paloma Beamer noted the use of NHANES literature for mixtures. She asked if the amounts of each chemical were considered in the algorithm. Dr. Wambaugh clarified that he only showed a paper on how they identify combinations of chemicals. There are several theories on how to best proceed with mixtures and concentrations. Work on the prediction of metabolic clearance and binding is in progress.

Dr. Gennings started by congratulating Dr. Wambaugh on a great discussion. She then brought up exposure forensics. She asked if sources of exposure could be identified if non-targeted assays were available for pregnant women's urine, serum, etc. Dr. Wambaugh shared that a STAR grant was provided to look at placental blood. There are several pieces that would come together. Within the gestational model, fetal cord blood can be predicted at that term. The STAR grant will assist with data generation and the models do the rest. Not all of the necessary pieces have been developed but are in progress. Dr. Gennings asked if, with the forensics part of it, they were trying to identify the chemicals so they have more than peaks (e.g., go back and link those to sources). Dr. Wambaugh agreed with this statement. If a peak is obtained with a particular mass and the chemical is in the database, it will give you the 18 chemicals that are close to that mass. Pathway and formulation predictions can then be run. That is what they call a forensics process because they do not have the portable data yet.

Dr. Somasundaran asked if, of the 3,000 chemicals needing chemical signatures, there was any coordination to determine who will research what. Dr. Wambaugh stated that Dr. Sobus would first determine who is already doing what. Each method has its blind spots. At the time of the meeting, it included getting everyone to the table. The work will then be divided. Dr. Bahadori stated that communication and data sharing are needed.

Dr. Stevens stated that a few years prior, they looked at all of their pharmaceutical data from their non-chemical studies and asked what things were the most correlated and likely to have an AOP. He asked if Dr. Wambaugh if consideration of the actual blood level versus accumulation was achievable in any of their models. Dr. Wambaugh responded that volume distribution can be predicted. Dr. Grace Patlewicz is a scientist in the National Center for Computational Toxicology (NCCT) that specializes in read across, and she works on incorporating toxicokinetic read across into the predictions. In the past, the volume distribution for thousands of chemicals could not be determined.

Dr. Weisel mentioned he noticed people trying to understand what is actually in products. He asked how they might be addressing the IT concerns. Dr. Wambaugh explained the fastest way to get the raw data is to mail a hard drive to RTP, North Carolina. There was just too much data to post it online and this approach is faster than downloading over any internet connection. If he was the manufacturer of a product, and he saw a summary that a specific chemical was in the product, he would want to see the raw data. This is on the drawing board.

Dr. McPartland asked if, in the graphic where Dr. Wambaugh showed the overlap between exposure and human equivalent dose, the human equivalent dose accounted for different life stages. She also noted that he mentioned that exposure prediction was in the population median. She asked about the 95th percentile. Dr. Wambaugh stated that in his work, they are looking at different life stages. From the exposure perspective, this can be achieved because it is built into

the PBPK and exposure models. The PBPK model can find the 95th percentile, but the exposure model cannot because the statistical modeling is challenging.

Demonstration and Evaluation

Dr. Richard Judson

Dr. Richard Judson explained that the Demonstration and Evaluation (D&E) project differs from the others in multiple ways. There are only three to four people working full-time on D&E, making it a small project in terms of personnel. In the project, they want to take risk assessment case studies for key partners and stakeholders and bring together data and expertise from other projects to be able to answer real-world problems.

Dr. Judson mentioned they have three big projects:

1. Endocrine Disruptor Screening Program (EDSP21): How can they use high-throughput screening methods to help? This included alternative methods for EDSP Tier 1 and streamlined validation approaches.
2. RapidTox: This task approaches the statement "We have a lot of chemicals we do not know much about" and asks how one brings all of these tools together to help.
3. CSS Dashboards

For EDSP21, they have to worry about estrogen, androgen, steroidogenesis, and the thyroid. There are high-throughput approaches for all. For estrogen, an estrogen receptor model paper and validation against uterotrophic assays is complete. That was the first time the Agency said *in vivo* tests could be replaced with *in vitro* assays. They then had good data for 1,800 chemicals and the estrogen receptor. They organized a project with 17 quantitative structure–activity relationship (QSAR) modeling groups around the world to build models and work across CSS to come up with a list of chemicals. People are exposed to around 40,000 chemicals. For the estrogen receptor, they can test or predict for every chemical people could be exposed to. For androgens, 1,800 chemicals were tested and put into a model. A similar QSAR project (CoMPARA) was also conducted on the 40,000 chemicals. At the time of the meeting, 30 groups had been brought in to help. For steroids, a high-throughput version of the standard tier 1 assay is available for steroidogenesis and has been run on 2,000 chemicals. Additional models have been developed in this area.

Across CSS, progress has been made for EDSP21. For the androgen receptor, a pathway can be thought of like a mini AOP. Dr. Judson noted there are many assays in which they can look at that. D&E is where uncertainties are brought together and modeled. They are comparing with a set of reference chemicals. For steroidogenesis, the pathway is well-known and a chemical can block this pathway by blocking any of the enzymes. With the assay they are running, all of the analytes are measured across the pathway. This provides better resolution on what is happening, but the data are more complicated. A modeling effort is also underway. For the thyroid, there are no laboratory resources available, so Tox21 partners have assisted by measuring thyrotropin releasing hormone and the thyroid receptors themselves. That started back to finding the entire thyroid AOP. Over the years, they have found laboratories to develop the assays, which will be

integrated in a systems model. These assays will help determine if a chemical is likely to be thyroid-disruptive *in vivo*.

Concerning streamlined validation, Dr. Judson stated for any of the assays, validation must be done. It is fraught. The international groups take years to decide if an assay is validated. If they have many assays, they have to develop a rapid validation approach. A key stumbling block is a list of reference chemicals, especially with a new assay or target for which there is a lot of history. There is an ongoing project for the androgen receptor to try higher-throughput methods. Dr. Judson explained the methods: method 1 included expert curation of the literature; method 2 involves automated literature mining followed by curation; and method 3 included mining of public sources (e.g., PubChem, ChEMBL, ToxCast, Tox21, etc.). Researchers are looking to see if they can use a high-throughput method and to produce a set of chemicals as good as those in method 1. This covers many targets.

RapidTox is a new work-in-progress project focused on the development of tools for screening level risk assessments. *In vivo*, *in vitro*, exposure, and toxicokinetics data are pulled into databases and dashboards. Users can look into the database and determine if there is high-quality data for risk assessments. It provides easy access to high-quality (high-tier) data as inputs to risk assessments, when available, and lower-tier data when higher-tier data is not available. If *in vivo* data are not available, a series of models are built that range from ToxCast assays to toxicokinetics to create a point of departure for a particular assay to high-throughput read across methods. This will be housed in the dashboard, which will be client-specific.

One case study Dr. Judson described was the Inerts Case Study with OPP. They were faced with public petitions requesting further evaluation of approximately 120 inert ingredients. The goal was to have a prioritized list (most to least concern) for further evaluation. This was an exposure example. The second case study he explained was the Office of Land and Emergency Management (OLEM) (formerly the Office of Solid Waste and Emergency Response) Case Study. There were approximately 1,500 chemicals nominated by OLEM and regions that were data-poor. The primary goal was to develop a list of quantitative screening levels with uncertainties and determine if tools can be provided for screening level risk assessments. Instead of saying they do not know, Dr. Judson provided some reasonable data to start with. The secondary goal is to have some type of hazard identification, fate and transport, and other key data. He noted they also have smaller projects with other stakeholders and collaborators.

The dashboard is a key way to push data out and make tools and databases available. Dr. Judson shared that one significant challenge is the growing number of databases maintained by principal investigators (PIs). The program is trying to hire someone to maintain all of the databases in the CompTox center. Web services is also available so researchers can access their data to make their own dashboards. They have their own dashboards and many models built off of the data.

Dr. Judson discussed the modeling project. They found that of the 40,000 chemicals, only about 3,000 chemicals have been put through a repeat dose toxicity study, which equals 5 to 10 percent. He noted they have to model their way out of that. They have had a lot of work building physical/chemical models to help across the AOP. Although the program develops many of the methods, legacy tools (from EPA or outside sources) are integrated where possible. As far as

interaction, D&E is small, but they spend a lot of time working and coordinating with other groups.

Discussion

Dr. Weisel stated the project looked like it had a key to interface with their partners and stakeholders. He asked if the goal was to eventually have a dashboard that is self-explanatory or intermediate. That could determine effort and if they have the resources to do what they are suggesting. Dr. Judson explained they were trying to do both. The problem is that the self-explanatory dashboard must be simple and risk assessment will never be simple. Dr. Weisel asked if they can get the information from them or if it would be too frustrating on their own. He asked which approach is better. Dr. Bahadori explained that was a good question to ask the partners. No matter how simple they make things, they need to have it constantly updated and their work is tailored. Dr. Weisel said setting up this two-way communication is crucial. Dr. Judson added that there is a tradeoff between building dashboards to be flexible enough to solve each problem. There might be too much IT effort invested when it would almost be easier to have an expert available to pick up the phone. Dr. Bahadori noted answers to a given question will be different between program offices and regions.

Virtual Tissues

Dr. Tom Knudsen, Dr. Sid Hunter

Dr. Tom Knudsen and Dr. Sid Hunter introduced themselves. Dr. Knudsen explained that the virtual tissue models (VTMs) project included an extremely ambitious and informative plan. The project has benefited from post-doctoral students. The progress has been incremental and there have been a lot of challenges. Biology is complicated. High-throughput assays are supposed to reduce the complexity of the system so they can be studied quantitatively. They want to put that complexity back and focus on cellular interactions and biologically informed models. These models tend to be driven by the biology, but there is a lot of integration.

The VTM project grew out of a virtual embryo project. Many of those working in the program have a particular interest in prenatal development. The question of how tissues are shaped in development is important when dealing with the embryo. That is a problem with the developmental effects of chemicals as well. They are trying to understand how those disruptions translate into phenotypes. At the tissue level, the unit of biology and function is the cell. The fundamental data that comes from ToxCast is at the cellular and molecular scale. In order to model the dynamics of the developmental system and morphoregulatory AOPs, the complexity has to be built into the system. Virtual tissues help to fill this gap and improve the ability to predict how chemicals impact human development. This is heavily covered in the children's environmental health research roadmap.

Dr. Hunter explained the project is focused on three areas:

- Morphogenesis: The research questions include "What are the cellular processes involved in development that are part of a high-throughput assay (e.g., morphogenic fusion,

epithelial-mesenchymal transition)?" Complex cellular interactions are necessary for development.

- Thyrotrophic Neurodevelopment: The first part is on the fetal physiome. Research questions include "How can one understand thyroid hormone availability and changes in a rapidly-developing system? How can one understand maternal thyroid hormones and their bioavailability and their changes across time? What does the thyroid hormone actually do (e.g., neurovascular unit)? How does one build environmental and computational models that begin to explain what is happening in human development?"
- Tipping Points: The first part is on microdosimetry. Research questions include "How does one begin to model intracellular concentrations in a dynamically changing world? The second part is on the state dynamics. How does one look at *in vitro* assays and the interactions between cellular responses to be able to predict a cellular homeostatic mechanism?"

There are also. Universities have received OCM-PT STAR grants from EPA. They are developing models and EPA is accepting them.

Dr. Knudsen explained that the idea of integration in the VTM project is to take *in vitro* data and *in silico* models and apply them to predictive toxicology with a focus on special dynamics and tissue reconstruction. The advantage of that in CSS is they have integration opportunities with other projects. Interactions are productive interactions and there are weekly meetings. All centers are well represented.

Dr. Hunter described morphogenic fusion as a critical embryological process. It is a delay or disruption underlying common birth defects (e.g., cleft palate, hypospadias, and spina bifida). Most tasks try to have both an experimental part and computational component (posters 13 and 14). That is an important process, so they assays are built that can use human cells. Workflow included starting the bioactivity profiles from ToxCast, building circuits, reconstructing the cellular dynamics, and building an agent-based model and simulation.

Dr. Knudsen described epithelial-mesenchymal transition as a delay or disruption underlying some congenital malformations (e.g., valvulo-septal heart defects). There has been interest in the same approach (i.e., building knowledge-based experimental models and integrating those into computational models). Through access of other databases, other classification models have been utilized to look at chemical disruptions and heart malformations. The heart has three layers at the initiation of the event. As they think about AOPs, they are going to change across time because of the sensitivity of the tissues. Instead of using a two-dimensional model, a three-dimensional model will be used that includes flow and other considerations.

Dr. Hunter explained the Human Physiome Model aims to build a comprehensive HTTK model to predict the impact of thyroid disruptors on thyroid hormone homeostasis during pregnancy and lactation. He noted the audience had heard about that in various forms already. A nonradioactive thyroid hormone metabolomics-based assay is being developed that measures different metabolites of the thyroid hormone and looks at transporter specificity. An important consideration is determining the capacity of the liver to take up and metabolize thyroid hormones. They are trying to bring the PBPK models down to the systems biology level.

Another aim is to bring the systems and bioreactors together in a microphysiological circuit and collaborate with one of their STAR grant recipients to look at the transport of T4 across the artificial blood brain barrier. Collaboration has been extremely successful.

In discussing the Neurovascular Unit, Dr. Knudsen said the task focused on what goes on in the early developmental stages. The goal is to knock down different targets in zebrafish and look at the structural and ultimate consequences of disrupting the thyroid hormone status. A post-doctoral student developed a computational model looking at vasculargenesis in the neuroepithelium and the development of the blood brain barrier. They work with collaborators who drive new models on regional differentiation of brain segments. Experimental and computational modeling are being used to examine and predict human brain development. Dr. Hunter explained they want to focus on the Zika virus by developing a general AOP model for microcephaly. Their focus is on the blood brain barrier and neurovascular disease. The hypothesis is that they do not occur in isolation and are actually tied together. Some of the models have been delivered while others remain under development. Putting the systems on a high-performance computing infrastructure so they are available and can be accessed efficiently is a challenge, but progress has been made.

Finally, the Tipping Points project looks at state trajectories that distinguish cellular adaptive versus adverse reactions. The computational model can help inform the modeling of some neurological networks. With the integration with OCM-PT STAR grant centers, one does not get the appreciation for the scale and scope of the biological and toxicological space covered by this work. Like the other projects, the VTM project is broad and interdisciplinary.

Discussion

Dr. Waters asked if the development of an AOP for hypospadias has been attempted in instances where there is a state of morphogenesis known to contribute to the development of hypospadias. An AOP for hypospadias could be used to inform evaluation for chemicals that cause hypospadias. Dr. Hunter replied that they recently published a systems toxicology paper that built all the available information on hypospadias and other male development issues. This information is boiled down to the critical pathways and five modes of action. A second paper discussed the cellular details of hypospadias and morphogenetic fusion in more depth. More complexity could be added to the models. For example, they could consider what happens if there is a 20 percent reduction in testosterone and the associated efficiency of the system. Pregnant women take statins and in combination with polymorphism and an androgen receptor the threshold can decrease to a number of concern. Dr. Hunter stated they start with an AOP, but are trying to understand the dynamics of the key events in the process.

Dr. Solomon asked if branching morphogenesis was considered. Dr. Knudsen explained that there was a project at the University of Wisconsin focused specifically on three-dimensional models of the acinar cells in the breast in the four stages of cancer development. Another project at Vanderbilt is focused on memory development. Those two projects teams do not communicate directly, but there are efforts to integrate the work where appropriate.

Subcommittee Discussion and Deliberation

Subcommittee

Dr. Stevens asked what they could do as a BOSC subcommittee for them to highlight the effectiveness of an innovative ecosystem mechanism to advance science. He noted the Agency seemed to be pulling in some of the best people in the world to get the science done. He guessed that would be costly. Dr. Bahadori stated everyone was building models. Dr. Knudsen went out and educated the community about doing the work and suggested they build the context. That is needed because the biomedical community is unaware of the challenges. It is an uphill battle and requires people on the team who have the presence in the community and are able to bring the information back to users. Dr. Stevens asked again what they could do as a BOSC to assist with cost-effectiveness. Dr. Knudsen replied that sustainability needs to continue and collaboration should be encouraged. There are challenges as developing and incorporating complex systems analysis. There is a lot of time spent troubleshooting. They want to think of ways they can incrementally provide useful information. The post-doctoral students developed great ideas. Dr. Stevens mentioned it was worth some commenting in the report. Their strength is the modeling. Having other staff who are skilled in the basic biology and the microphysiological systems is cost- and time-ineffective. It makes more sense to put the money into the biological systems outside and focus on the things they do well. Dr. Weisel stated the amount of integration externally and internally is great and he would like to highlight some key examples.

CSS Poster Session and Genius Bars
Poster Session #1

The BOSC CSS subcommittee members attended the poster session and genius bars that addressed SeqAPASS, AOP-wiki, ECOTOX, and VT-LS.

Subcommittee Discussion of Charge Questions

Subcommittee and Tina Bahadori

Dr. Mark Wiesner, a BOSC CSS subcommittee member, joined the meeting. He is an Environmental Engineer with Duke University.

Dr. Somasundaran asked the group for reactions, thoughts, and impressions from the posters and genius bar interactions with the CSS researchers.

Dr. Johnson visited the VTM posters, 13 to 17. His top line impression was that this part of the program is getting there and moving ahead. However, they are not exactly there yet. Some of the projects are really exciting. It is the future of what is going on in the biotechnology and pharmaceutical industry. He referenced poster 16 and noted that the high content imaging screening described was not being done on a continuous basis. The results are usually captured at 1-hour, 24-hours, and 72-hours. Dr. Johnson expressed concern that this interval approach could be missing some types of events like initial events or repair mechanisms. With certain types of compounds, static types of information gathering may miss these events. Dr. Johnson encouraged consideration of what the subcommittee learned from toxicogenomic databases, which were found to require a more continuous approach. He did not know if CSS is using processes to collect data on a continual basis.

Dr. Vorhees asked if Dr. Johnson was talking about gene expression in particular. Dr. Johnson clarified that he was referring to anything with imaging as an endpoint. Dr. Vorhees replied that poster 4 talked about HTT assay development for neurotoxicity. She said they currently look at individual endpoints but are moving toward continuous collection over a 24-hour period. Dr. Johnson expressed interest in this work and noted that he would visit this poster.

The group discussed whether they are sharing concerns and impressions or starting to frame the report content. Dr. Somasundaran had planned for the group to go through the sections.

The group continued discussion of the VTM posters. Dr. Waters said she observed many instances this year where there were clear connections to the modeling of outcomes and building the bridge to test hypotheses in the literature and in AOPs. What she did not see was the researchers' thinking about the chemical evaluation component and how they could use the reference chemical to test the hypotheses within the models for whether the AOP is correct. Evaluation is needed to determine if the model recapitulates what the chemical is doing. She noted huge advancement since last year. Dr. Somasundaran agreed that researchers had come a long way in the last year.

Dr. McPartland asked for clarifications about the AOPs. Dr. Waters clarified that CSS has some models developed based on a constructed AOP, but the people who built the model were not clear if the AOP had been validated. The model is trained on that basis but if it has not been tested and the AOP hasn't been validated, then one will get out of it what one puts into it. Dr. Waters suggested that the next step is to characterize the quantitative relationship between the reference chemical exposure and the key events to confirm that the perturbation of those key events is actually recapitulating the adverse outcome.

Dr. Stevens said he has heard the term "validated" as well as the term "endorsed" in reference to AOPs. Dr. Bahadori clarified that OECD endorses AOPs. Endorsement means that the AOP has entered the language of the scientific community that builds consensus around testing strategies. It has undergone baseline validation steps and the international community can build on it. There are five or six steps. The process is part policy and part scientific. She said that the kind of validation Dr. Waters referred to is different and within the space of science validation.

Dr. Bahadori said that what CSS presented was a view of a slice of time and simply provided the subcommittee with an understanding of the CSS program's current work. She asked if the BOSC observed any significant gaps in the science or any low hanging fruit that would add value to the program. CSS is also interested in issues of integration.

Dr. Waters said an additional area of integration was VTM with blood brain barrier work that examines the biological effect of chemicals. This work could be looped into AOPs as an exposure parameter because there are effects on the blood brain barrier that affect exposure.

Dr. Bahadori agreed this has not happened as of yet because of the complexity of the project. However, there has been interest expressed during project team meetings. The most important validation exercise for that community is validating the models in the context of epidemiological data. This provides a higher biological complexity. Dr. Waters noted the team needs to walk before they can run.

Dr. Somasundaran reiterated that CSS has made much progress in 1 year and that he was impressed. He suggested that CSS researchers could learn from research in other fields. For example, there is some excellent work on coalescence of bubbles which might be useful in understanding cell interactions. Consideration of other disciplines might be missing from the current portfolio.

Dr. Bahadori said that CSS only received 71 percent of the budget that was presented to the BOSC last year. The budget cuts applied to everyone, but CSS fared better than most.

Dr. Stevens shared that he spent time learning about the AOP Wiki at the Genius Bar and while viewing the posters. He thought the quality of the CSS science he learned about was outstanding. He felt that the researchers were more connected to the mission and impact of their work. He spoke about the findings from a computational analysis of pesticides that found they were not always binned where they were supposed to be binned by the experts.

Dr. Stevens found the science of the AOP Wiki to be strong, but he expressed concern that the tool is lagging behind the aspiration. In the examples he viewed, he thought delivery of the web architecture was out-stripping the delivery of endorsed AOPs to capture the risk assessment community's attention. He would have expected more commentary.

Following up on integration, Dr. Stevens noted that AOPs are knowledge-based models, not computational models. He asked where might CSS take modeling of biological systems and the computational cheminformatics systems and merge them into hybrid models. He acknowledged CSS had a strategy that he learned from Dr. Judson. Dr. Stevens suggested that that strategy needs to be more up front, even though it is very aspirational. Dr. Waters pointed out that it appeared that the AOP Wiki researchers were not aware of this strategy. Dr. Bahadori responded that this comment was on point. She said CSS was building all of their computational capacity on a small group, NCCT, but they recognize that the approach is not sustainable due to their small size. CSS is exploring ways to expand on capacity, but everything is limited by the resources being invested in building things out according to strategy.

Dr. Stevens acknowledged the challenges. He clarified that the focus of the AOP presentation was on demonstrating the wiki. When Dr. Stevens asked about systems modeling and network based approaches, the researcher responded positively. The researcher articulated a vision for how to create knowledge models, see how data fit the models, how to independently model biological systems, and how to investigate their fit with the data driven models. It appeared that the AOP Wiki discovery and development group is operating independently of the strategy.

Dr. McPartland noted that there is a small community contributing knowledge to the AOPs. She asked the researchers how to increase the number of individuals who are feeding knowledge. Dr. Bahadori acknowledged that the AOPs are not getting the desired engagement.

Dr. McPartland asked about potential opportunities to motivate people to engage in developing the AOPs. She asked about the possibility of working with Environmental Health Perspectives or the National Library of Medicine. Dr. Bahadori said they would get a lot of putative AOPs, but they would not be developed. The issue is that the community is not engaging. EPA was starting to pull back, but maybe it will start clicking.

Dr. Klaper pointed out the interest by the ecotoxicology community. The researchers go where they receive funding. She asked if a STAR grant is a possibility. Dr. Bahadori said CSS is exploring allocating funding into a STAR grant to put resources out there to develop AOPs. There is also a computational RFA. Society of Environmental Toxicology and Chemistry (SETAC) is having a Pellston workshop. Dr. Bahadori said the idea of those workshops was to create momentum. Ultimately, it does require funding. The two relevant STAR grant RFAs are to build out an organotypic cell model and to build AOPs.

Dr. Stevens stated that AOPs are an integral part of the strategy, but if all the customer base sees is the AOP Wiki, there could be a disconnect with the small number of AOPs and low engagement. He suggested that the situation puts the strategy in jeopardy because it does not illustrate the quality. Framing the topic better might work. Dr. Bahadori agreed and said the comment is helpful.

Dr. McPartland asked if the OECD community requirements for AOPs are constraining. Dr. Bahadori replied that CSS pulled away for a time from the OECD committees. It is starting to re-engage with an aim to drive efforts. She said OECD endorsement of AOPs is of value, but CSS is trying to make the process more action oriented. She was receptive to comments about bringing the science strategy more out front and evaluating and better optimizing the OECD process. CSS could be more aggressive in how it engages with OECD. Dr. McPartland asked if EPA can build its own AOPs and then present them to OECD. Dr. McPartland expressed curiosity about whether the ability to deliver AOPs was dependent on OECD. Dr. Bahadori discussed how transition away from animal models requires consensus through OECD. EPA's regulatory side prefers OECD buy in. CSS and National Toxicology Program (NTP) are advocating to break the log jam. The barriers are capacity. In the TSCA space, there is a lot of science required to catch up to move from simple QSAR models to new high-throughput methods. A lot of work has to be protected behind confidential business information firewalls. Dr. Bahadori described the time it took to develop endocrine disrupting chemical assays and how much longer it will take for more complex thyroid pathways.

A subcommittee member said she spoke with Dr. Judson, who told her he was asked to help with a Superfund case for Region 8, to develop "poor man's reference doses" or points of departures based on high throughput data and compare these data to what they had been using. In general the point of departure values CSS developed were generally biased low. Dr. Bahadori said that Dr. Judson is an informaticist who can provide a range of points of departure with uncertainty. The number used would depend on the risk context. Dr. Tom Burke has written papers about needing to walk away from bright lines. RapidTox will give any value available and quantify the uncertainty with some confidence.

The challenge is that people who are using a reference dose, live by that number. With lower numbers, they get pushback out of concern that it is application of a precautionary principle. There has been much more interest and engagement.

Dr. Beamer asked the researchers what would be the output of a successful relationship, but the response was uncertain. Dr. Beamer wondered if there might be a way to engage with programs and regions to see what CSS can do for them. Someone must be willing to take a risk. Dr.

Raffaele from OLEM said there is a lot of misunderstanding by the researchers about what the regulators need and, similarly, there is a lot of misunderstanding by the regulators about what computational toxicology can produce. Success will only be reached by working together through the process.

Dr. Solomon brought the conversation back to the subcommittee's reactions to the posters. A subcommittee member noted that CSS exposure research was exciting and asked what would be a marker of success. Dr. Wiesel agreed that the work on exposure research in poster 23 was interesting.

Dr. Bahadori said that CSS is trying to figure out how to judge scientific success and merit and how EPA can show success. The old method of counting the number of publications no longer works for EPA. CSS is exploring some interesting approaches, such as identifying different organizations that are using the information and looking at gray literature citations of the studies. The utilization of the research is also one of the measures of success (e.g., a citation in regulation, use in regulatory decision in the United States or internationally). EPA ORD is seeking a new way of discussing the impact of their science and meeting the goals. The BOSC Executive Committee will guide the program.

The first charge question is about whether CSS is doing right science, and can CSS separate that from the barriers to getting there. The general answer from the subcommittee was that the answer is yes, but the floor was opened to subcommittee members to respond.

Dr. Klaper said she thought the program was missing high-throughput sequencing, metabolic assays. She asked about thyroid pathways. Dr. Bahadori replied that there are other efforts that were not in the current budget cycle. The plan is to onboard water soluble chemicals (e.g., glycophosphate), develop new assays for volatiles, and initiate an effort to develop a validated assay for developmental neurotoxicity.

Dr. Klaper asked about transcriptomic screening approaches. She wondered if high throughput screening will help identify assays to go after and what assays will not be sustainable to go after. Dr. Bahadori replied that transcriptomics projects are in place, but there is nothing to show the subcommittee yet.

The subcommittee turned back to charge question 1, "Are we doing the right research? Taking resource limitations into considerations, are there any significant scientific gaps?"

Dr. Stevens stated that he thinks the science is right. The only gap is that the AOP work *is in vitro* focused and should have an *in vivo* focus. There does not seem to be an investment in modeling complex biological systems. He felt that a new assay is less helpful than modeling the complex biological systems.

Charge question 2 focused on integration, "Based on prior feedback from this Subcommittee, over the past year, CSS has focused on further integrating the program within and between projects. Please comment on the progress. Is the integration approach right? Are there other areas that should be enriched?"

Dr. Stevens suggested that a bigger issue than integration is that potentially doing too much on all the right topics might result in not doing well enough on a single spot or integration. Dr. Stevens asked where there are obvious opportunities to have an impact. Dr. Bahadori responded that the CSS has VTM for human health. CSS has ecological research that is complex systems modeling but admitted that the communities are not talking with one another.

Dr. Gennings said she was impressed with the program. She brings an epidemiological perspective and detected some frustration with epidemiology data for assessment. She is curious about how to develop untargeted assays to detect effects on vulnerable populations such as children and pregnant women. If there are strong and repeatable epidemiological data, the toxicity (both *in vitro* and *in vivo* data) need to be in the same framework. Dr. Bahadori responded that Dr. McPartland had recently hosted a meeting that convened a community of epidemiologists to tackle the issue. She said there was a lot of passion, but agreed that the toxicity testing frameworks do not align with the epidemiological work. Dr. Burke has been working on rebuilding relationships. For example, EPA is increasing its engagement at the American Public Health Association conference. Exposure data are useful. The Children's Health Exposure Analysis Resource (CHEAR) and Environmental Influences on Child Health Outcomes (ECHO) public databases should be available and helpful.

Dr. Gennings said she had a good discussion about cumulative risk assessment with a CSS researcher. She suggested that in thinking about achieving real improvement, there might be an opportunity to move beyond risk assessment and use market forces. Dr. Bahadori responded that there have been efforts to democratize the science and educate. CSS must support EPA's mission and regulatory efforts, which must use risk assessment. She said Dr. Burke has prepared a manuscript recasting risk assessment in public health space.

Dr. Weisel noted there might be a gap in integration with partners for RapidTox. He expressed concern about putting the information out and telling the partners to use it. He suggested providing a website with information but suggests that partners reach out with the researchers when they are ready to use the information.

Dr. Bahadori described the ToxCast dashboard experience. Partners tended to want dashboards for a specific decision context, which needs a lot of engagement. Dr. Franzosa is working with the pesticide team.

Dr. McPartland suggested that it would be good to guide the epidemiological community in how they could mine the data for hypotheses to test in the field.

The only way to have regulations is to have a risk assessment. The problem is lower than what is needed.

Dr. Solomon brought up the posters on read across (posters 18 and 19). She confessed she was a little disappointed. She had hoped to have contributed more, but was struggling with what to recommend. She acknowledged it is a very popular approach now. Dr. Solomon felt that the endpoint of body weight was too general of a response to be useful. Dr. Weisel thought the work would integrate well with what CSS is doing in exposure. He thought the read across work was

isolated. Dr. Bahadori agreed and said the effort is to develop a framework to implement read across. She noted that more information would be presented tomorrow.

Dr. Solomon said the exposure posters were amazing. She specifically pointed out the valuable work in posters 5 and 6 and acknowledged the great progress since last year.

Dr. Solomon noted that the DSSTox database is due to become public very soon, but it is backlogged. Dr. Bahadori noted that CSS is dealing with issues related to the number of dashboards and databases and their integration.

Dr. Stevens noted read across is very structurally based to date and an incremental add on to the QSAR approach. He suggested that read across can happen across biological systems.

Wrap-up and Adjourn
Ponisseril Somasundaran and Gina Solomon

Dr. Solomon moved forward with suggestions for topics for members to draft charge question responses around:

- Drs. Waters and Johnson: VTM
- Drs. Stevens and Klaper: AOP, will address OECD as it relates
- Dr. Vorhees: point of departure in risk assessment
- Dr. Gennings: mixtures, connecting with epidemiology world
- Dr. Beamer: what incentives to working with barriers
- Dr. Solomon: exposure, read across, significant progress compared to last year on thyroid, neurotoxicity

The meeting was adjourned for the day.

Thursday, November 17

Welcome and Review of Day 1

Dr. Ponisseril Somasundaran, Dr. Gina Solomon

Dr. Somasundaran stated that yesterday's meeting was great. He reviewed the names of the presentations from yesterday's meeting. The poster sessions and demonstrations were also valuable. He reminded the participants to identify themselves before speaking and to wait to be called upon.

Dr. Solomon stated that Ms. Fleming was working to pull together copies of what was written up yesterday. Since there was no internet connection in room, the documents could be shared via thumb drives or Ms. Fleming could provide print copies for everyone.

Dr. Somasundaran stated that introductions are not needed and he read the titles of the day's presentations.

Overview of Day 2

Dr. Tina Bahadori

Dr. Bahadori stated that on the biology side everything was framed around the pathways framework. On the chemistry pollutant and environmental exposure side, the life cycle perspective is also important. The nanomaterials project teams and chemistry teams have the emphasis in the Agency on regulating the molecule in its native form. However, in exposure studies it has been found that exposures actually occur down the lifecycle of the material and there are transformations in that process that contribute to the nature of exposure. With that framework in mind, data is collected in a way that informs a health protective strategy more than what is natural in a regulatory environment. This is also where the group can frame approaches to assess cumulative and aggregate exposure.

The emerging materials project is primarily focused on new materials. The focus is on the physical and chemical properties of the material. The nanomaterials team has led an effort to begin to compile characterizations and properties around nanomaterials that will inform that perspective. The sustainable chemistry project and the life cycle and human exposure project both have a strong focus on chemistry and exposure in both human and ecological receptors. In this way, the group can help the Agency address the issue of selection of a safer alternative, which is an alternative decision processes.

The ecological risk assessment topic also straddles the complex systems topic area and LCA. Those projects will be presented today and all of them, with the exception of nanomaterials, are new projects. All of the projects have adopted new approaches.

Today's genius bars include several dashboards. Anna Lowit, from EPA OCSPP OPP joined the group and will speak on the panel later this morning.

Life Cycle Analytics Topic Area Research Project Deep Dive

Sustainable Chemistry

Caroline Stevens/Todd Martin

Dr. Stevens stated she was one of the co-project leads for the Sustainable Chemistry project. She noted she would provide the overview of Tasks 1 and 3 and Dr. Martin would provide an overview of Tasks 2, 4, and 5. In the project, sustainable chemistry is defined. The focus is typically on human toxicity, but the sustainable chemistry project is taking a broader and holistic view by thinking about human exposure, health hazard, ecosystem exposure, and environmental persistence. Sustainable chemistry is about developing tools that can predict the potential human health, ecosystems, and environmental impacts of a chemical just based on its molecular structure.

Dr. Stevens explained there are several research drivers where strategies are needed to evaluate the potential for environmental and human health impacts from new and alternative chemical products prior to their introduction into commerce (e.g., before the chemical is manufactured, in the planning stages, etc.). Researchers have considered what information can be provided by the molecular structure. This is important in the review of pre-manufactured notifications and pesticide registration/re-registration. The sustainable chemistry team is also prioritizing the testing of existing chemicals, such as the selection of TSCA work plan chemicals. They look at alternatives assessment, the Design for the Environment, and incorporating Safer Choice. They also focus on life cycle analysis and work with the Sustainable Materials Management Program within OLEM.

Much of the project focuses on the development of web-based tools. The four main tools are the Chemical Knowledge Toolbox, CompTox Chemistry Dashboard, Alternatives Assessment Dashboard, and Chemical Transformation Simulator. These tools are hosted in two clouds: NCCT (in RTP, North Carolina, USA) and NERL Quantitative Exposure Domain (a CGI Federal Cloud in Arizona, USA). Despite the separate clouds and different tools, they are highly linked through the use of web services to transfer data. There are many planned connections through these web services and they support for several tools being developed in other CSS programs as well as outside the CSS program is anticipated. For example, within the NCCT cloud, the CompTox Chemistry Dashboard serves up data to the RapidTox tool. Within the NERL Quantitative Exposure Domain, the übertool Eco Models were developed as part of the Ecological Modeling project and the LCA and HEM Human Exposure Models were developed as part of the Life Cycle - Human Exposure Modeling project. EPI Suite web services are also under development at OPPT. Dr. Stevens mentioned the tools were designed with a modular approach. Layered architecture is used with reusable components. A web services approach is also being used where one must have an Application Programming Interface (API) which describes the ways you can serve up data and models via web services.

Dr. Stevens discussed Sustainable Chemistry Task 1, which is led by Dr. Tony Williams from NCCT, and focused on developing cheminformatics architecture. There are two main focus areas within this task including the CompTox Dashboard, which is a consolidated web platform that

provides chemical information look-up, models, and model predictions. It provides linkages to both Agency and public resources and it is already a publicly-available resource (Version 1 launched at the American Chemical Society [ACS] Fall Meeting in Philadelphia). It is receiving a lot of attention and used inside and outside of EPA. The second area of focus is cheminformatics and data mining approaches for exploring the alternatives testing landscape. It is focused around developing tools for structure-based data mining and modeling in support of toxicity assessments. ToxPrint Chemotypes are used to examine the coverage of chemical inventories and bioactivity enrichment patterns across the large datasets that are becoming available.

Dr. Stevens provided a screenshot of the dashboard and explained the user could enter a chemical name/CASRN and a wealth of data would be displayed about the chemical (e.g., structural representation, identifiers, molecular formula, etc.). There are tabs at the bottom to provide different data layers (e.g., computed and measured chemical properties, exposure and use patterns, QSAR-based PBPK and toxicity predictions, etc.).

Dr. Stevens described plans for the future. For the dashboard, Dr. Stevens explained that API/Web Services are in development as well as support for literature handling. This provides a way to pull in data from published journal articles and reports. The project is working on real time predictions for physiochemical property estimation as well as support for ambiguous substances (e.g., mixtures, polymers). It is difficult because these are things that might not have a definite chemical structures, so standards and protocols need to be developed for handling those. This also includes deeper integration to the Agency's databases and tools. For the cheminformatics and data mining approaches for exploring the alternatives testing landscape, knowledge-based repository delivery is planned. This illustrates how the ToxPrint Chemotypes have been associated with the assay data and use categories in the data layers. Dr. Stevens noted there would also be automated workflows to support the use of ToxPrint Chemotypes for read-across and data mining.

Dr. Stevens explained that Task 3 is focused on the development of the Chemical Transformation Simulator. This work is led by Dr. Eric Weber from NERL. The Chemical Transformation Simulator is a web-based system for predicting transformation pathways and physiochemical properties (from both the parent and the transformation product) of organic chemicals. Three workflows were developed: calculating chemical speciation as a function of pH for the parent chemical, the calculation of physiochemical properties (e.g., EPI Suite, Spark, T.E.S.T., and ChemAxon-based tools), and the generation of transformation products. The idea is to predict the transformation products and then pull together the physical chemical properties for both the parent and transformation products.

For the Chemical Transformation Simulator, Dr. Stevens explained they have a Beta version that was delivered in September 2015 (available behind the EPA firewall). For FY17–19, they plan to have a linkage to the EAWAG pathway prediction system for aerobic biodegradation product predictions (originally developed at the University of Minnesota), additional reaction libraries for phototransformations and anaerobic biodegradation, batch executions for all workflows, and implementation of web service data changes with the CompTox Chemistry Dashboard,

Alternatives Assessment Dashboard, and the übertool models for the Ecological Modeling project. Prototypes are under development and a production version is to be delivered in 2018.

Dr. Martin explained that Task 2 focuses on developing predictive models for AOP, MOA, and MIE potency. In FY16, the product was to improve hazard screening models for pesticide risk assessment. A paper on this work is in review. It covered mechanism-based analysis of acetylcholinesterase inhibitory potency of organophosphates, carbamates, and their analogs. For FY17, the product focused on improving hazard screening models (biologically relevant QSAR models) for toxic chemical risk assessment. Dr. Martin is working collaboratively to predict pesticide acute rodent toxicity using two-dimensional chemical descriptors and target species classification. Datasets are broken down to use submodels to predict toxicity. There is also work on acute aquatic toxicity MOA prediction methodology for pesticides and other chemicals. This work is focused more on pesticides.

Dr. Martin explained that Task 4 focuses on sustainable molecular design. In Task 4, the focus is on development of a framework for identifying a more sustainable synthesis route for a chemical identified as an alternative to an existing chemical of concern. It applies a retrosynthetic approach coupled with proven peer-reviewed literature examples. He noted the goal was to develop a green chemistry reference knowledge database. They would go out in the literature, find sustainable synthesis routes for different classes of chemicals, and then try to use EPA's knowledge about green synthesis routes to develop this database. Then, one could look at molecules based on their molecular descriptors and break it down into pieces. There is a translator and a cross index tool to determine which descriptor routes are relevant to generate different synthesis routes for that chemical.

In FY16, the product was to apply the framework to the case study of organophosphates. In FY18, the goal is to put this into practice in a web-based tool. The goal is that dashboard users can click a button to bring up a synthesis route and the chemicals involved for a specific chemical. It serves as the beginning portion to determine the chemical reaction ontology that allows one to make connections to the structure, reaction pathways, and the construction restraints. This ties into the LCA/Human Exposure Model (HEM) project because it allows one to determine which chemicals are involved in the life cycle inventory. This will be part of the dashboard. Alternatives are compared, but users might also want to compare the chemicals involved in the synthesis of that chemical.

Dr. Martin explained that Task 5 pulls together the other tasks. The first task has several parts (e.g., CompTox Dashboard), but mainly curates datasets of chemical identifiers, structural features, and properties. Molecules are broken down into structural features. Task 2 is focused on the development of biologically relevant toxicity models. Task 3 allows for the prediction of transformation products and physiochemical properties. When evaluating different alternatives, it is important to understand how chemicals break down in the environment or how they metabolize in humans. One has to look at the toxicity of the metabolites when comparing alternatives. Task 4 will allow for the generation of routes for sustainable synthesis and provide the chemicals involved during the synthesis route. Task 5 involves the comparison of alternatives in terms of human health, ecotoxicity, and physiochemical properties.

The FY16 product for Task 5 was the framework document for the Alternatives Assessment Dashboard for evaluating chemical alternatives applied to flame retardants for electronic applications. In FY17, as a first step, Dr. Martin noted they wanted to make a web-based version of Toxicity Estimation Software Tool (TEST) to integrate into the CompTox Dashboard to make predictions quickly for new chemicals inside the web tool. More people would use it, and in the future, those predicted toxicity values will need to be compared to alternatives and feed into other EPA tools. In FY18, they want to make a web-based version of the Alternatives Assessment Dashboard. In order to do that, Global Harmonized System (GHS) data, scores, and endpoints are needed. To get at those numbers, public databases and QSAR models can be used. For some endpoints, the use of QSAR methods might not be the best approach and read across methods could be used for analog searching. This should tie in with Task 1 in the CompTox Dashboard.

For the sustainable chemistry project, there are several deliverables:

1. Tools for analyzing and mining chemical space including structure-based feature sets, chemical clustering schemes, similarity indices, and analog identification methods,
2. Predictive models for estimating toxicity, persistence, bioaccumulation and transformation potential based on chemical structural features and inherent chemical properties,
3. Guidance on Sustainable Molecular Design (SMD) of chemical products, and
4. Alternatives Assessment Dashboard

Discussion

Dr. Klaper mentioned that when she spoke with the ECOTOX database folks, they wanted to integrate with PubChem. In slide 4, a different network of databases is included. Dr. Klaper noted she did not see the ECOTOX database, which was an important development to integrate toxicity information. Dr. Martin explained that some of that data does fit in there (e.g., data from ECOTOX) and NCCT includes those databases in their own databases. It might not be a live capture, but it is in there. The conversation is underway and a link from ECOTOX should be provided by the end of the year. Dr. Klaper pointed out the newer emphasis on other measures besides LC50 (i.e., the lethal concentration required to kill 50 percent of the population) in ECOTOX is also important. She asked if the work under Task 2 is similar to Carlye's models. Dr. Bahadori replied that it was and this work will be moved into Dr. Villeneuve's project. It is a better fit in the AOP project to enhance that linkage.

Dr. McPartland asked about the extent to which high-throughput ecology data developed in NCCT would be integrated in, for example, the Alternatives Assessment Dashboard. It seemed at one point it was, but in the description of FY18, it focused more on mining QSAR models. Dr. Martin stated that one of the ways he tried to integrate that data was by including the binding to the estrogen receptor. One of the toxicological endpoints is estrogen receptor binding and that was achieved through high-throughput data and descriptors. For that endpoint, it will be used, but it is still in the early stages. It might not have a direct tie in for some of the toxicological endpoints, but there is ongoing modeling to use those high-throughput screening numbers. The second phase is to look at the exposure side. One needs to know the concentration in the

environment that would be dangerous relative to the exposure. People do that by looking at the responses from high-throughput. Conversions are used to find the *in vivo* dose. The high-throughput data can be used to find the toxicity level of concern in the environment. The other way to use high-throughput data is to estimate binding the estrogen receptor.

Dr. Beamer suggested the project team consider how to better present their work so that the integration is clearer to the subcommittee. She asked if the IT infrastructure presented challenges to the cloud base and web services. Dr. Beamer asked how other project areas could learn from their work. Dr. Stevens responded that they were not working with existing tools. Bringing in a legacy model is difficult. Within CTS, they are putting a wrapper around it and there are ongoing efforts to redesign their work to more efficiently serve users. They are building up the data structures to make it easy. Dr. Bahadori noted these are plans. Dr. Beamer observed that there are still barriers in implementing these plans.

Dr. Weisel asked if, in the alternative discussion, they were going to include the amount of material, stability in the environment, and differences across age. Dr. Martin responded that these considerations were incorporated in the second stage of comparison. They want to see what the dose rates are. The first step is on the toxicology side. Dr. Weisel suggested the first step should be on the exposure side.

Life Cycle - Human Exposure Modeling

Jane Bare/Paul Price

Dr. Paul Price presented the Life Cycle-Human Exposure Modeling (LC-HEM) which is a joint project between EPA's NERL and National Risk Management Research Laboratory (NRML). The purpose of the project is to integrate chemical exposure knowledge and life cycle analysis to assess the exposures to chemicals which occur over the life cycle of products and to support sustainability assessments by improving life cycle analysis. The LC-HEM project includes tasks organized around the collection and organization of data, research on modeling human behaviors, and software designs to efficiently use available data and to characterize the uncertainty from data gaps.

Two sections of the project build on the HEM and the Consumer Product Life Cycle Analyzer (CPCLA). Both parts of the project will deliver software. The first version of HEM will be completed next year, and CPLCA will be completed 2 years later. Each will be modular and the modules will have value. Dr. Price stated that the types of exposures over the life cycles of products will be evaluated, including near field and far field pathways. They have created descriptions of populations and are looking at aggregate exposure for other consumer products, which include not only dose but also background exposures. They are building by extending SHEDS-HT (CSS RED), the NCCT dashboard (CSS sustainable chemistry), and research on composition of products. The HEM Module will feature agent-based models (ABMs) of exposure-related behaviors. ABMs combine elements of decision theory, computational sociology, and Monte Carlo methods to gain insights into complex processes by simulating the behavior of agents obeying objective rules that govern how they interact with models of systems and other agents. The ABMs of use of consumer products are based on the concept of products

fulfilling individuals' actual and perceived needs. They have developed an approach to integrate the HEM and LCA which involved mapping exposure information for risk assessment to the classic life cycle assessment approach.

The output for near field exposures would be a classic description of dose distribution for a single consumer product totaled together. The output could give the information in terms of units that LCA requires. The analysis can be split by subpopulation (e.g., children, adults, and professional users).

Moving further into improving the LCA process, the projects are oriented to make the information more rapidly available. Right now LCA takes too long. The project will integrate government sources of other LCA information (e.g., energy use and water use). The effort involves both a top down data mining project and a bottom up simulation project.

Project challenges include identification, collection, curation, and organization of data on product compositions, releases to the environment, habits and practices for consumer products; generation of longitudinal descriptions of human behavior and exposure; and paucity of data to support comprehensive chemical coverage. Elements of project integration include the following. LC-HEM is using data generated by the RED and Demonstration and Evaluation projects. It is also jointly working with Emerging Materials on extending CPDat to include nanomaterials. HEM outputs are being used in CompTox dashboards.

Discussion

Dr. Johnson said that the research is really exciting and spectacular. He asked if CSS could identify the probability of success over time periods. The probability of success might decrease over the years. CSS could perform this analysis to determine how to move probability of success up, like some budget, staff, or new technologies. Dr. Weisel encouraged the research team to make sure the formulation information is updated. The formulations may change, but the name may not change.

A subcommittee member asked how CSS will validate the model. Dr. Price replied that they will use the Consolidated Human Activity Database (CHAD). Dr. Weisel recommended that they need to go beyond CHAD.

Dr. Vorhees asked if there is an acute versus chronic exposure or a single maximum exposure, and how it accounts for ethnicity and sample sizes. Dr. Price replied that SHEDS addresses a single day, but they are trying to get to 1 year. They could predict shorter time periods than that, but the goal is to estimate chronic exposures. The peak exposure could be used to assess acute exposure.

Dr. Vorhees asked about the National Institutes of Health (NIH) consumer product database and if it would be clear in the LC-HEM software where data came from. Dr. Price replied they are using the NIH information and are building in transparency of data sources.

Emerging Materials

Dr. Kim Rogers

Dr. Rogers presented on CSS project 18.02, Emerging Materials. The project is structured around three tasks: Database and Informatics, Decision Support Framework and Case Studies and Functional Assays and Predictive Models. The third task is broken into two parts: Quantified Process Rates and Alternative Screening Assays (Aggregation, Dissolution, Genetics, Metabolomics, and Viability) and Transport and Fate Models.

The database project has three deliverables. The first, database structure, is complete. The second part is to populate the database with ORD nanomaterials research and lastly, develop decision tools. It will be compatible with other databases and eventually made public. The data support framework is a living document. The base document has been written and submitted for review and once complete it will be used to guide research efforts. The group will examine fate and transport exposure and effects of products along their life cycle and disposal. Thus, the need to examine transformation and far-field exposures measured thru ecosystem indicator species. The critical node is important because that is where nanomaterials might leave the product and humans or environmental organisms are exposed.

A feature of the program is functional characteristics assays. Nanoparticles can have various combinations of coatings, which make them act completely different. Functional characteristics include aggregation, surface binding, dissolution, which allow us to predict how groups of particles or products will behave. The case studies show how the life cycle format is used to guide the direction of our studies. It goes from consumer products to the human alternative assays and ecosystem indicator species.

Some examples included titanium dioxide in sunscreen and exposure to swimming pool water or micronized copper-treated lumber in decks and fences. Micronized copper-treated lumber is a nano-enabled product with huge volume use. Most of the micronized copper particles are in the micron range, but the size is dependent. Two exposure pathways exist for the carbonate: wiping or contact and breathing sandy dust or sawdust. Most are in the micron range, but for treated wood, many of the particles are in the less than 30 micron range. Industry has created a challenge by producing a treatment of the wood (e.g., stain versus polymer treated) affecting how much exposure occurs.

There is also interest in downstream effects. Researchers have studied the disposal and waste stream and have looked at different types of silver nanoparticles, coded with different charge features. Each behaved dramatically different. Researchers are looking at differential gene expression and discovering that there are several different pathways affected. The important feature is to examine what these nanoparticles are doing to change the cell function. Most nanoparticles are coded by industry. In order to understand how to model these in environmental settings, there is a need to determine how they behave as they enter. It is important in understanding changing nanomaterials is to put them in circumstances where they could be found in natural environment (i.e., with sunlight, graphene oxide breaks down in smaller fragments that are not well defined).

In summary, a lifecycle approach is key to identifying critical nodes for product use and disuse. The focus is on products (building materials and food containers) and release scenarios (near field and far field exposures) to develop specific process rates and identify potential biomarkers of an adverse effects. Program offices and regions have asked for the development of science based and comparable assays. Lastly, nanoparticle research requires the integration of a variety of expertise.

Discussion

Dr. Johnson inquired where the laboratories are located. Dr. Rogers replied that the projects and products have multi-laboratory collaboration in RTP, North Carolina; Cincinnati, Ohio, Athens, Georgia; Las Vegas, Nevada; and Corvallis, Oregon. Dr. Wiesner inquired if there is a strategy for a module for predicting the source quantities. Dr. Rodgers stated that there is a project to integrate data from all the nanomaterials databases and make predictions on human exposure. Another part of that project is to identify and analyze every product for nanomaterial information to better understand what people are actually using.

Dr. Waters asked about the assays and biomarkers of adverse effects and what is being identified. Dr. Hughes stated that investigators are looking at different organ systems *in vivo*. Dr. Stevens inquired whether one of the gaps in nanomaterials is not enough physical descriptors and whether that was a key deficiency. Dr. Hughes responded that one of the problems in relaying nanomaterials into QSAR is that nanoparticles behave in different and unpredictable ways depending on their coding and size. He states they are working with the Program Offices, OECD, and the International Standards Organization (ISO) to come up with simple and validated ways to characterize and create a standard technique to be used by industry.

Ecological Modeling

Matt Etterson/Tom Purucker

Dr. Matt Etterson presented this project, which aims to evaluate the ecological significance of observed or predicted effects on individual organisms. EPA cannot limit its focus to individual-level exposure or effects because it can lead to inaccurate risk estimates and errors in environmental management decisions (e.g., over- or under-estimation of risk). CSS will build on what is known about perturbations of individual-level endpoints e.g., (survivorship, fecundity, and behavior) to predict population, ecosystem, and landscape responses.

EPA has a long legacy of using ecological models for a variety of regulations, including the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Endangered Species Act. This work will impact current approaches and try to maximize use for different regulations.

There are many dimensions to address for ecological modeling. There are different chemical categories (e.g., pesticides, household uses), loading scenarios (e.g., agricultural application, residential use, and municipal treatment), exposure media, taxa/species, internal dose metrics (e.g., biomarkers and cellular responses), organismal effects, and population effects (e.g., reduced population growth and competing/relative risks).

With respect to modeling ecological exposure, there are two tasks: one focusing on internal dose and the other on external dose. The internal dose task will develop methods for predicting *in vivo* exposure to organisms with an emphasis on methodologically challenging compounds (e.g., high K_{ow}, low solubility). The external dose task will develop methods for predicting spatiotemporal distribution of both chemicals and ecological receptors (i.e., species) in a heterogeneous environment.

The ecological effects modeling has two tasks: one on ecological effects and one on endangered populations. The ecological effects task will develop methods for predicting the effects of chemical stressors on animal demographic rates. The task on endangered populations will create and evaluate a system of linked models to be used by EPA risk assessors to conduct spatially-explicit, population level risk assessment for threatened and endangered birds exposed to pesticides.

The modeling will be applied with an aquatic case study. The case study will explore transitioning from the current EPA process towards probabilistic risk assessment for threatened and endangered species. Monitoring data is available to ground truth the predictive fate and transport models.

The project would also fill gaps. For example, the Agency does not have good amphibian models. For effects assessment, CSS is considering extrapolation, going from effects and pull back into 'omics levels with the goals of bridging across species and evaluating reliability. The team is exploring the possibility of pushing the available data to inform population level inputs and develop "toxicity translators." Key products in FY17 include population modeling tools to support pesticide risk assessment and selection of an amphibian dermal model for pesticide registration.

The project has many stakeholders and collaborators including OPP, Region 9, and Office of Water. Outside of EPA, U.S. Fish and Wildlife Service and the National Oceanic and Atmospheric Marine Fisheries Service, U.S. Department of Agriculture, USGS, State of California agencies, University of California - Davis, and Ohio State University.

Discussion

Dr. Johnson asked how much data CSS has and how much has to be developed for the model. Dr. Etterson responded that it depends on the program. There are a lot more data for pesticides compared to industrial chemicals due to the difference between the statutes governing them. There might be some translation of models or data models for industrial chemicals.

Dr. Johnson added that there is also a need for translation for different species. Dr. Etterson agreed and mentioned that pollinators are quickly being addressed to go through the review process for pesticide chemicals.

Dr. Klaper noted the complexities of the project. She asked if there are specific directions or processes for how the team decides what projects to attempt because she assumed it is a small group.

Dr. Etterson responded that they have a legacy of models that require curation. One way to focus is to plug a hole by modifying models. They look for ways to maximize contributions across the landscape of needs and bring legacy models online to help with high throughput work. Dr. Klaper asked if the team identified anything they are missing. Dr. Etterson said they have to set priorities, which have recently been bees and other megafauna.

Dr. Wiesner said he was impressed with the project. He wondered if the project needs to be broader. He asked if there is any work on nutrients or the microbiome in the soil. Dr. Bahadori said these topics are not addressed in the CSS research program. Dr. Wiesner asked if any work is being done on ozone crosscutting effects.

Dr. Etterson reiterated that priorities are guided by the opportunities to fill gaps. For example, a limited set of life histories are available for birds. EPA has not been able to address aquatic wading birds, raptors, or mammals due to lack of data.

Dr. Stevens identified links to read across. He asked about the investment in sentinel species. The information could provide information on comparative systems biology to support read across for complex biological systems. Dr. Etterson replied that species extrapolation is being addressed but at a low level. This work integrates well with AOPs because it provides apical endpoints that inform population effects assessment.

Subcommittee Discussion and Deliberation

Subcommittee

Dr. Stevens stated there were two discussion topics that interested him. The first was around software development. There are so many things being developed, but the trap is when they build these tools, they are burdened with rolling the tools out and dealing with customer complaints among other issues. He asked what they were going to do to support and sustain the tool given that IT support has been identified as a key deficiency. His second comment is that he agrees the AOP strategy could help support complex systems, but it is a knowledge management infrastructure and not a systems data generation strategy. He noted he was not sure how complex systems modeling was done *in vivo*. He would like to see future plans for the investment in genomics going toward real complex *in vivo* systems even if they are not human. It could help the subcommittee with the read across problem. Dr. Somasundaran stated there are many other variables, such as temperature and microbes, and size and shape of the nanotubes.

Dr. Weisel asked if they could have a two-minute description from Dr. Bahadori on the role of CSS in the ecosystem. Dr. Bahadori stated most their ecological portfolio is in the Sustainable and Healthy Communities (SHC) and Safe and Sustainable Water Resources (SSWR) subcommittees. Nutrient cycling is across all programs with CSS playing a small role in the chemical domain. Most of the work is in the complex systems domain. It is a minute piece of the much larger ecotoxicology domain, but CSS believes it is the most transformative piece. One of their challenges moving forward is to feed this into the ecological research that goes on in the rest of the organization. CSS is a small piece of this pie.

Dr. McPartland asked if it was CSS's impression that there are others within the national research programs to fill the holes. Dr. Bahadori said it is philosophy. In CSS, they are trying to develop approaches and methods to drive the thinking; they are not trying to solve all problems. They want to develop methods to help inform the data. For example, in SHC, they do a deep dive in a risk assessment for one chemical. That covers all five years of their research and it is comprehensive. CSS is not trying to go there. They want to put their energy in coming up with methods, tools, and AOP- and chemistry-informed approaches that allow the users make decisions faster rather than to make perfect decisions. TIM/McNest and the landscape approach are significant increases in the ability to do things faster and more realistically. That is consistent with the goal of the program and where CSS differentiates with other programs that do more deep dives into risk assessment.

Dr. Klaper mentioned there were a few missing parts. For the ECOTOX database, there was a lot of information that needed to be populated. Dr. Bahadori noted ECOTOX was a needs-driven and expert-curated database at first. Once they grabbed onto it, they realized it could not sustain everyone. CSS is building it from scratch again. In the past, it was just LC50. Dr. Klaper stated it needed to be linked into other things and more measurements of apical endpoints past mortality. It is still limited and focused on the ecological side only. Dr. Bahadori said it is not just ORD money being put into it and the program also works with the regions for funding as well. Dr. Dan Villeneuve has a young PI that understands the landscape. Dr. Klaper noted PubMed and PubChem are interested, but it needs to be pushed.

Dr. Stevens stated he thought CSS was doing all the things right to support the risk assessment mission. To illustrate, when he redesigned the toxicological approach, the systems biology literature that gave them the best guidance was the literature propagated by evolutionary biology models. They can look at network-based models. It requires a systems level data set, but for the species of interest. That provides the read across capability using computational biology methodologies, which is different from AOPs, risk assessment support, etc. That is in fact a foundation for read across risk assessment. Dr. Bahadori clarified that the AOP project thinking would happen in the complex systems science. When Dr. Stevens noted he did not see it there, Dr. Bahadori stated it was not there yet.

Dr. Johnson asked if STAR programs could be put in this field. Dr. Bahadori mentioned those were just funded and academic research of that complexity is limited. Dr. Stevens mentioned a group at Indiana University proposing to do just that. Bahadori stated although they would look into that, something along these lines would hopefully be seen at next year's Subcommittee meeting. Dr. Klaper commented that in reading the STAR grant proposals that go out, they seem to be convoluted. Dr. Bahadori agreed.

Dr. Weisel asked that in concerning the ecological piece, they had talked about the ecotoxicity portion. They call external dose what he called exposure. That needs to be expanded as well. Different from humans, there is a temporal period that goes into play. Back to the CompTox Dashboard, there are things in there that are great, but they only saw one tab on that screen. That one tab was the easiest. It is a massive thing to do properly. He noted this was something they needed to address.

EPA Program and Regional Offices

Program and Regional Offices Perspectives on CSS

Carole Braverman, Region 5 and the Great Lakes Restoration Initiative (GLRI) (by phone/webinar)

Dr. Braverman, the Regional Science Liaison to the GLRI, stated that the Great Lakes are phenomenal and contain 84 percent of North America's surface freshwater. There are new contaminants in the Great Lakes watershed, but they are finding ways to identify them. There are five focus areas of the FY15–19 plan. The GLRI is charged with better understanding emerging contaminants in Great Lakes fish and wildlife. The problem is that real world exposures are to mixtures, not single chemicals and there are still unknowns. CSS is helping to address this problem by using high-throughput screening tools and applying them to environmental mixtures. The GLRI is working in partnership with CSS to help us target monitoring and integrate effects-based monitoring approaches to account for unknowns and the integrated effects of mixtures. The focus is on pathway-based endpoints to gain better insights into the type(s) of chemical(s) driving the effects observed. Case studies are being conducted to move these approaches from research and development to practical application. A large scale, multi-year effort is ongoing to detect the most relevant Contaminants of Emerging Concern (CECs) and assess their impact(s) on fish and wildlife. The GLRI is also looking at different types of land use to targeting the mixture of CECs and how they correlate with land use to determine priorities. This is a highly leveraged effort from multiple government agencies and academic institutions. The GLRI is optimistic with the progress they are making, and that is made possible by the partnership with CSS and the ability to make faster decisions

Betsy Behl, Office of Water

Ms. Behl explained areas of focus include an update of the aquatic life guidelines to update methods, explore fast track methodology, and explore the toxicity of cyanotoxins. Regions and states have concerns about cyanotoxins and there is limited data. The Office of Water hopes CSS's tools will help understand the toxicity of those compounds. The other area is work with the EDSP and participation in those workgroups to help inform our assessments. Other areas include our ability to use a variety of different methods to prioritize chemicals for criteria. OW is leveraging projects where CompTox tools are being used to develop metrics of effects and looking to other programs to develop these CompTox tools.

Dr. Weisel inquired about stakeholder's acceptance of the use of newer methods. Dr. Behl stated they have initiated that discussion in a workshop and have had other conversations with the SAB. At EPA, there is acceptance with additional recognition of advancements from 1985 and getting some of these tools into our methodology.

Marie O'Shea, Region 2

Dr. O'Shea is the lead region coordinator for OCSPP. It has been 6 weeks since taking over as lead region and Dr. O'Shea anticipates her role will be to help CSS obtain additional input and collaborate on partner-oriented work groups, planning teams, as well as additional case studies in

multiple regions. She stated that many emerging issues begin in Region 2 and it will be a beneficial relationship. Microplastics is one of her regions top priorities. Dr. Somasundaran asked what states made up her region. She stated New York, New Jersey, Puerto Rico and Virgin Islands make up Region 2.

Tala Henry, OCSPP Office of Pollution Prevention and Toxics

Dr. Henry, from OCSPP Office of Pollution Prevention and Toxics, addressed the subcommittee from the standpoint as a CSS customer. She identified areas of opportunities in AOP area linkages. She stated the need for further collaboration in the area of rapid exposure and functional use. Rapid toxicokinetics looks immediately promising but needs further collaboration (i.e., need to know more about the reference chemical list and understand how much it covers in our universe). Read across is used frequently. There is a need to know more about the reference list. The office is open to the use of high-throughput methodologies to address the volatiles and particulates. In the area of RapidTox, there are efforts to redesign one of the rules to collect toxicology data as an order under our new legislation. There was a demonstration project where a list of ten chemicals was submitted and within 2 weeks, RapidTox was run and sent back. There is concern on explosion of the dashboards because they cannot put a proprietary chemical out on the web and need to find a way to put these tools inside our CCBI firewall.

Literature services are being adopted, including NHEERL's ECOTOX database. Dr. Henry's group is looking to NCEA to adopt the Health and Environmental Research Online (HERO) data searching and gathering, but also have another tool, ECOSAR and the ASTER tool from NHEERL. The chemical transformation product tool is also helpful. In the green chemistry area, there is overlap with a functional use project. Dr. Henry stated that they work with nanomaterials daily and would appreciate a presentation on nanomaterials. She said they also work in the rapidly growing biotechnology field (i.e., genetically engineered compounds) and there is a significant need for assistance and training on all tools. She encouraged collaboration and early inclusion in the development of products and processes.

Dr. Stevens inquired whether a gap exists in the writing requirements for use of the dashboards for internal customers and external users. Dr. Henry responded that progress is being made to fill those gaps. Dr. Bahadori added that the end user changes under each regulatory construct, thus the data and dashboards are developed at a higher level and applicability. Dr. Vorhees asked for elaboration on what is being done with complex mixtures. Dr. Henry replied that the CompTox Center has been getting robust nomenclature, but many are discrete chemicals. It could be a mixture as simple as xylene. Dr. Bahadori stated that this work falls under one of Dr. Tony William's assignments after being embedded in their domain. Dr. Klaper asked whether transformation products are considered in the regulation and if so, are they are considered in the assessment. Dr. Henry confirmed that is occurring.

Anna Lowit, OCSPP Office of Pesticide Programs

Dr. Lowit gave a review of her program office and the types of chemicals that they cover such as antimicrobial products, conventional pesticides and bio-pesticides. The group does human health and ecological assessments. She discussed the tools used by the ecological side of her group as

well as the human health side of the group. The translator tool is used to work with endangered species assessment. The ECOTOX database is used daily by the OPP group. Eventually they will get the überTool to integrate all of their tools to make their work faster and more efficient. They have a poster that will show their collaborations on the human health side. RapidTox is used with two case studies and it has a lot of promise for the OPP. The AOP project is important for some members in the department who have participated with AOP reviews. She suggested that her group would like to see development of tools on the eco-side and work to improve information flow from ORD to OPP.

Stan Barone, OCSPP Office of Science Coordination and Policy

Dr. Barone gave a high level overview of his office and their role. When his group needed to screen and prioritize 10,000 chemicals they turned to ORD for help. Much of their department's data is in silos so now they are in talks with ORD about being able to access all of the data sets regardless of how different the data are. They want to use the RapidTox tool to interrogate all of their datasets at one time. There is a need to use computing power to make data work. He stated that training on the use of the tools is critically important as well as staffing and human resources. He wanted CSS to know that models and tools will be continuously improved, provide version control, and good documentation.

Bruce Duncan, Region 10

Dr. Duncan stated that a shared vision between CSS and the regions is important. His group has used ECOTOX and QSAR and is excited to use new versions. He urged CSS to find areas where the end users can be inserted into the processes of tool development early on. Impact at the regional level is also important. He stated that the group should get regional input on advisory groups and regions need to identify what their issues are and prioritize them. He would like a continued effort to jointly map out what collaboration looks like between ORD and the regions with a focus on model interoperability.

Kathleen Raffaele, Office of Land and Emergency Management

Dr. Raffaele explained that the RapidTox tool is used to develop a tool for use to risk assessors to find information about chemicals that have no values. They need the information to respond quickly to emergencies such as a chemical spill. The information is needed so that they can understand a potential risk at any site. They are making good progress on this project. Exposure modeling efforts would also be of use to OLEM.

Wendy O'Brien, Region 8

Dr. O'Brien provided an overview of her work and how risk is assessed in an emergency situation. Many chemicals that her group encounter in an emergency do not have toxicity information associated with them. RapidTox helps fill the gap when they have no information to assess toxic risk. The tool helps them do their job as they interface with the public. She stated that scientists and the end-users have built good bridges between each other to understand each other, but work is still needed in the area of public involvement and engagement. She asked how emergency clean ups, timely efficiencies, and cost reduction can be measured. It is also important to make sure that EPA's assistance to the public can be measured.

Following the panel session, the subcommittee jointly agreed is was a good idea to gain their perspectives.

CSS Poster Session and Genius Bars
Poster Session #2

CSS Scientists

Concurrent Genius Bars (RapidTox, CPDat, Chemistry Dashboard)
CSS Scientists

Subcommittee Discussion and Deliberation
Subcommittee

The subcommittee discussed the following topics relating to projects demonstrated in the Genius Bar and posters.

Dr. Wiesner discussed the need to develop data platforms for more functional assays for nanoscale chemicals. Dr. Klaper mentioned the database should be linked into CompTox database and the information is not that different. The information just needs to be described and an approach is needed on how to handle the front end. Dr. Johnson commented on the series of dashboards, which is a great product that is user-friendly and hyperlinks into data sources. A new application will be released which is more updated and searchable than CASRN. He commented on the concepts on using the chemo-type versions which is incorporated into the data. He stated that Dr. Ann Richard has done an excellent job and her work provides a strong foundation. Dr. Johnson concluded that the right science is being conducted and in the right way. Dr. Johnson stated that embedding software problems is the key and IT will be instrumental. The gap is in the development stage only because of the timeframe. Read across is extremely important.

Dr. Weisel commented on the need to document measures of success and to dedicate a specific way to cite it, so it becomes a much easier search like web bias. He mentioned that CSS should consider the final result before developing new exposure tools. Dr. Beamer stated that-in terms of output and outcomes, outputs are clear, but further clarification is needed on outcomes. She commented on the use of ECHO and CHEAR to evaluate the next steps beyond *in vivo* studies.

Dr. Gennings noted her interest in looking at the chronic low dose issues and mixtures occurring over time. Dr. Bahadori responded there is need to explore integration of epidemiology experience. Dr. Gennings suggested this might be a STAR grant opportunity. Dr. Klaper inquired about the strategy of the ecological modeling team and whether they should move into spaces other than pesticides. Dr. Bahadori stated that all the models are developed in collaboration with OPP and focus on pesticide risk assessment. She explained the use of resources and expanding RapidTox ecological risk assessment.

Dr. Solomon suggested the need for more information on STAR grants, LCA, and human exposure modeling. Dr. Weisel suggested integration into exposure and would like to see more integration into the toxicology side. He stated that evaluating the products and their use will identify what endpoints you need to understand. Dr. Bahadori discussed the process of budget planning and prioritization and the request for application (RFA) timeline.

Dr. Bahadori described the STAR grant process. It used to be that EPA put out its intentions, but it was pulled back because EPA's budget was uncertain. CSS has ideas for nine RFA topics. More funding is being allocated to the organotypic culture model (OCM) centers. These centers use pharmacokinetics and high-throughput modeling to build models across species. There are also several on exposure modeling and collecting exposure data. She stated that her preference is to fund fewer projects, but provide more funding to those projects.

Dr. Stevens praised the research execution by the CSS program. The matrix organization and success speaks to the program's leadership across the regions and centers. CSS is doing a great job delivering their work in a focused manner.

Dr. Stevens asked to return to the theme of *in vivo* complex systems modeling. The ecotoxicity arena is fertile for this type of modeling. He asked if CSS can collect sufficient data to execute sophisticated complex systems modeling. He encourages pursuing this work through STAR grants. He also mentioned that many of his concerns about the burden of software maintenance were resolved after talking to Dr. Judson. They are modular.

Dr. Stevens made a final comment that he found the posters to be dense with information. Some researchers had a tendency to explain fairly simple concepts using dense language. To communicate effectively, researchers need to find ways to communicate their work clearly. Another subcommittee member agreed with this statement and noted that some of the slides were also dense with information. The researchers should mitigate their tendency to rely on jargon, or even make up jargon, when describing simple processes. This issue could be addressed with coaching.

Dr. Stevens said he was really impressed with the program, and he considered himself to be a pretty skeptical person. He expressed his congratulations.

Dr. Waters added that last year the subcommittee challenged CSS to describe integration between different components. She thought that the thyroid example served as the essence of what CSS is trying to accomplish. Admittedly, the parts do not fit together well. This may be because they were not designed to. However, the team has learned more about why it is difficult to do so and have a better understanding of how to adjust their approach. It is a perfect example of demonstrating how to get the whole team to do that in an integrated way. Dr. Waters noted that this process has just started, but is successful and working.

Dr. Waters asked where the strategy for transcriptomic integration fits within the AOP framework. She mentioned a project on biomarkers and biosignature for cancer where genomics was supposed to be an AOP without a link. The researcher said this work was down the road. That team would benefit from talking to the AOP group because that team seemed disconnected from AOPs. The team is trying to find their space. Dr. Bahadori responded that the project is like an incubator and is just budding. Dr. Waters suggested that all of those efforts need a strategy describing how the outputs would be used in the AOP framework.

Dr. Solomon thanked the subcommittee members who provided written comments after the first day of the meeting. She asked the subcommittee members to read the drafts tonight and be prepared to add to these drafts and discuss them tomorrow. She added that it is not clear at this

time if the subcommittee will be done with their responses to the charge questions at the end of this in-person meeting or if another conference call will be needed. Ms. Fleming said they will need to decide tomorrow if another conference call is needed in order to get the *Federal Register* notice out in sufficient time given the compressed schedule.

Public Comments
Ms. Fleming stated for the record that she did not receive any public comments. She opened the floor up for public comments. There were none.

Subcommittee Wrap Up and Adjourn
Ponisseril Somasundaran and Gina Solomon

Dr. Solomon reviewed the topics and assignments. Dr. Waters will address the issue of genomics/transcriptomics and provide more detail on the thyroid example. Dr. Stevens will address complex systems science, ecotoxicology, IT infrastructure/software development, and communicating scientific information more clearly. Dr. Beamer will write about the end of life piece of the life cycle (e.g., recycling, reuse). Dr. Beamer, Dr. Johnson, and Dr. Klaper will provide comments on the STAR grant program (e.g., positive about VTM, any deficiencies, and the pursuit of complex systems modeling and ecotoxicity species). Dr. Gennings will refine her draft after hearing Dr. Vandenberg present on Day 3. Dr. McPartland will prepare a summary of the subcommittee's observations during the engagement session on the morning of the second day of the meeting and build on what Dr. Klaper and Dr. Beamer reported. Dr. Dr. Somasundaran will address nanotechnology. Dr. Klaper will address complex mixtures and cumulative exposure. Dr. Wiesner will address the LC-HEM project. Dr. Johnson will address the use of chemotype information, the chemistry dashboard, and the effort on curation of Chemical Abstracts Service (CAS) numbers. Dr. Weisel noted the need to integrate exposure and LCA to help direct work on alternate chemicals.

ORD is seeking feedback on approximately three "top-line" specific recommendations rather than a list of twenty recommendations. Dr. Bahadori requested feedback from the subcommittee on measures of impact.

Friday, November 18

Welcome and Review of Day 1 and 2

Ponisseril Somasundaran and Gina Solomon

Dr. Somasundaran stated that the subcommittee was ready for the HHRA presentation. The subcommittee received some summary documents by email. Ms. Fleming stated that ICF was working on compiling the summaries and would provide them to the group before the breakout sessions.

Dr. Bahadori clarified that Dr. Vandenberg was providing an update as opposed to a review of HHRA. Dr. Solomon stated that the subcommittee would hear from the HHRA program and then discuss the charge questions.

Human Health and Risk Assessment (HHRA) National Research Project Update

HHRA Update

Dr. John Vandenberg, HHRA National Program Director

Dr. Vandenberg began by stating that he was pleased to be at the meeting. He listened to the discussions by phone yesterday, so he added a slide to his presentation to respond to some of the comments that he heard. Dr. Vandenberg reminded everyone that it had been a full year since the group met. The HHRA program was at the interface that actually moves things directly into decision making. His group had a portfolio of approaches that included the development of methods and the application of new methods, including new science. His program has four major components. The Advancing Analyses and Applications is the one that they focus on for the BOSC. The main product lines are: Integrated Risk Information Assessment (IRIS), Integrated Science Assessments (ISAs) and Community and Site-Specific Risk. There are four topics and nine HHRA projects responding to partner priorities. The major focus is on Cumulative Risk Assessment Methods and Applications, Advancing Hazard Characterization and Dose-response Methods and Models, Applying Emerging Science to Inform Risk Screening and Assessment, and Risk Assessment Support and Training. This work is important because it shows how the group advances the science not only within the Agency but more broadly to a larger community.

IRIS Assessments, IRIS Update, ISAs, and Scientific/Regulatory Support and Provisional Peer-reviewed Toxicity Value (PPRTV) Assessments are the major areas of work for the HHRA, and they perform assessments to support the decision makers. Every year, the HHRA produces 12 Provisional Peer-Reviewed Toxicity Value (PPRTV) Assessments. All of the assessments receive internal review by EPA scientists and external peer review by independent scientific experts. There were currently 345 PPRTV assessment documents available online at the time of the meeting; however, nine chemicals have provisional values that are based upon new types of data and are in the appendix.

HHRA provides emergency response and support to Agency priorities. Types of support provided included:

- Reports to Superfund Technical Support Center and Ecological Risk Assessment Support Center,
- Rapid risk assessment response to emergent situations (e.g., Gold King Mine, Colorado),
- Technical consultation and support on Agency priorities (Denka facility in Louisiana), and
- Participation on Agency workgroups.

In response to BOSC recommendation from the previous summer, HHRA has made iterative and integrated approaches to foster understanding and trust of new techniques the group is looking at systematic reviews. They anticipate expanded assessment to portfolio in support of new TSCA as they characterize utility and as emerging applications mature.

The HHRA website provides links to all of their projects (IRIS, ISA and PPRTV). The HERO database contains more than more than three million references. Other tools that can be accessed from the website include:

- Benchmark Dose Software (BMDS) Modeling website and training system,
- EPA's-Expo-Box Website (EXPO-Box) and database,
- Ecological Risk Assessment Support Center (ERASC) website, and the
- Risk Assessment (Risk) Web Portal collection of human health risk assessments website and databases.

FY16–FY17 essential software support will involve development and maintenance of support tools for HERO, BMDS, ExpoBox and the IRIS website. Webinars and training on ExpoFIRST would appear in FY17. Various workshops for risk assessment training were located in Brasília, Brazil; Kuwait City, Kuwait; and Alexandria, Egypt. The web implementation three modules would come up in FY17. These included Risk Assessment Basics; Laws and Regulatory Foundation for Risk Assessment; and Overview of Human Health and Ecological Reference Values.

Other outreach activities created to encourage partner engagement were the creation of a monthly HHRA Bulletin, IRIS program updates on activities as needed to provide periodic updates on new BMDS versions as well as periodic messages sent out on EPA-Expo-Box. Partner membership in accessing these outreach resources has drastically increased. HHRA is committed to support and engage its stakeholders by:

- Providing a portfolio of assessment products for improved public health,
- Identifying issues and advances approaches to arrive at solutions,
- Applying new technologies and data to refine analyses,
- Supporting communities with cumulative risk characterization of multiple stressors on human and ecological health, and
- Educating and engaging stakeholders to build capacity.

Discussion

Dr. Somasundaran asked whether the Agency is learning from interactions among various global communities. Dr. Vandenberg stated that he recently attended an ozone conference in China, which provided an appreciation for the United States and their protection of the environment. Dr. Gennings inquired about the strategies to use the epidemiological data to inform studies and the evaluation of co-pollutants. Dr. Vandenberg stated that the epidemiology data is a priority and exposure data helps influence how the epidemiology data is interpreted. Biomarkers are also valuable and provide further. He stated that the Clean Air Scientific Advisory Committee (CASAC) has reinforced the importance of the exposure assessment to interpret the outcome measures in epidemiology studies.

Dr. Klaper asked how ecological risk assessments fit into human health risk assessments. Dr. Vandenberg explained welfare effects and how they fall into a secondary standards, specifically in the Clean Air Act.

Dr. Vorhees asked about the PPRTVs, the appendix values, and the peer review reaction. He requested clarification on why these values are located in the appendix and not in the main document. Dr. Vandenberg responded that the Agency is still evaluating some of the approaches, like QSAR and read across, but wanted to provide information on which chemicals to look for as well as stimulate the Agency to get the additional research needed to derive a final value. These additional nine values help set priorities for site managers. Dr. Vandenberg will inquire about the peer reviewers' comments.

Dr. McPartland suggested that the provisional appendix values could be used like a case study, and a good exercise would be to review them in parallel, while testing the new approaches. She also commended the HHRA on building the AOP from the top down and inquired about the challenges on the interaction between CSS and HHRA and how they can leverage one another. Dr. Annie Jarabek stated that Steve Edwards is also working on the arsenic, and they are evaluating more generic AOPs. Dr. Vandenberg commented that the Agency has the benefit of a close working relationships. National Program Directors meet weekly across multiple levels of the organization to have "cross talk" specifically on assessment and more broadly on how the Agency is thinking about data.

Dr. Johnson inquired, on behalf of his students, whether the Agency uses citizen scientists for data collection. Dr. Vandenberg stated that the Agency is in discussion with other federal agencies on new sensor data and recognizes the importance of citizen collected data. Lots of issues complicate this topic (i.e., the quality/validity of data from different sensors, the accuracy of the equipment, quality assurance, and privacy issues.) The Air, Climate, and Energy (ACE) program has been working with Google street view cars as a platform for the collection of real time data.

Dr. Stevens asked if HHRA coordinates with NTP regarding study design and data in topics such as chrome rubber. Dr. Vandenberg verified that there is a federal representative from the Agency to attend those meetings and they also help disseminate that information to the entire research community.

Dr. Gennings inquired about the work being done to establish reference doses for biomonitoring within the Agency. Dr. Vandenberg stated that HHRA is doing source attribution to calculate the source strength. Dr. Bahadori confirmed that CSS is comparing the biomonitoring data at an internal level to confirm PBPK data.

Dr. Vandenberg hoped that this information provides the subcommittee with a comprehensive overview of HHRA's efforts. He stated that staffing and budget concerns are major issues. Dr. Stevens asked if the BOSC should consider focusing more on HSRA next year, broad or "deep dive, or focusing on the interaction and relationship between the CSS and HHRA. He stated that the StRAP is high-level and the identified focus would affect the pre-read information. He inquired whether the BOSC should write up comments regarding CSS's mission to achieve risk assessment goals. Dr. Bahadori discussed a proposal by Deborah L. Swackhamer, the chair of the BOSC, for an additional charge question and the use of alterative data in the pesticide risk assessment.

Subcommittee Group Discussion of Preliminary Findings and Recommendations
Subcommittee

The subcommittee discussed how to organize the breakout groups. Dr. James Stevens mentioned that some topics fall under all agenda topics and objectives (e.g., AOPs). Dr. Solomon suggested organizing the breakout groups around the agenda as well as the four topic areas. She thought AOPs should remain where they were, but AOPs should also be mentioned in other sections. They should focus in on a topic area in the compiled text document and stitch together the fragments to create a coherent chunk. They could then come together with those chunks to create bigger picture comments as a group. The four topic areas included chemical evaluation (e.g., ToxCast, Rapid Exposure and Delivery, HTT), complex systems science (e.g., AOPs, Virtual Tissues Models, ECOTOX), LCA, and translation and knowledge delivery (e.g., CompTox).

The breakout groups were:

1. Chemical Evaluation: Donna Vorhees, Katrina Waters, Chris Gennings, Ponisseril Somasundaran
2. Complex Systems Science: James Stevens, Rebecca Klaper, Dale Johnson, Jennifer McPartland
3. LCA: Gina Solomon, Mark Wiesner, Rebecca Klaper, Ponisseril Somasundaran
4. Translation and Knowledge Delivery: Paloma Beamer, Jennifer McPartland

The subcommittee breakout groups discussed and drafted text responding to the charge questions.

Discussion of Outstanding Issues, Review of Draft Report, Review of Timeline and Assignment of Follow Up Activities
Subcommittee Breakout Group Leads

The subcommittee reconvened and reviewed the draft write-ups submitted to date. As a whole, the subcommittee provided input into each of the sections provided from each of the subgroups' documents.

Dr. Solomon pointed out the following areas of agreement from the subcommittee: 1) we recommended research around thyroid and neurodevelopment and progress was made, 2) our recommendation were taken with a broader approach and took a more comprehensive look, and 3) the need to take a broader look at the assays, on boarding of assay battery and using the high-transcript transcriptomics.

Dr. Johnson inquired whether the CSS program has identified the key assays. Dr. Bahadori responded they are being evaluated space by space. The subcommittee and Dr. Bahadori discussed the topic of high-throughput transcriptomics. They also discussed the utility of the subcommittee's evaluation and if it was more useful before or after a contract is in place and work has begun.

Dr. Stevens stated the read across of species is an important problem. Dr. Waters addressed the recommendation on how there was no unifying strategy presented on how data would be used or anchored to the AOP framework, and gene expression as assays themselves without relationship to function or endpoint.

Dr. Solomon expressed reservation on the use of approaches being used as a Tier 0 and the potential of closing of other areas of biological space. Dr. Bahadori expressed concern regarding the need to access 85,000 chemicals and the efficacy of using the strategies available. She also reiterated the need to onboard strategies because there is a lack of data and TSCA requires evidence of adversity before gathering data.

Dr. Waters discussed the topic of assay attrition. Dr. Stevens stated it would be valuable for CSS to develop a balanced strategy to both retire existing assays that might not add sufficient value to the program while bringing on board new assays that add important biological content to the hazard identification mission. Dr. Gennings discussed her comments regarding mixtures and the benefits of the Great Lakes Study to prioritize mixtures.

Dr. Stevens summarized the Complex Systems Science write-up, which split the topics into three categories: integrating complex science across species, virtual tissues and epigenetics, and AOPs. He also pointed out that for highly conserved biological response pathways, it is important to understand similarities and differences in biological response networks from *in vitro* data and models to both *in vivo* read across phyla and classes. This will also be important when mixtures of chemical compounds are added to screening efforts and predictions and validation of additivity, synergism, or reduction of effect are needed. Dr. Beamer discussed that CSS leadership is encouraged to chart a roadmap for how complex systems science can contribute to the ecotoxicology risk assessment read across challenges, children's environmental health, and the larger populations.

Dr. Stevens acknowledged the "elephant in the room": the AOP section and the issue of EPA endorsement. Dr. Wiesner suggested the use of the term EPA candidate versus endorsed. The subcommittee discussed AOP strategy and AOP Wiki content and recommended a change to the slides to "What an AOP is today? And what is our strategy for tomorrow?" These models will become quantitative when an AOP becomes a PBPK model. He also discussed that IT resources are limited.

Dr. Solomon summarized what was written for the LCA section. Dr. Wiesner stated there was a useful map of the CompTox dashboard, but he would like to see a roadmap that shows how it all fits together along with a timeline. Dr. Wiesner suggested that the Emerging Materials section focus on nanomaterials and be broken into two parts, 1) emerging research and materials and 2) database tools and information. Dr. Bahadori stated that biotechnology, genetically modified organisms (GMOs), pesticides, and toxics will be part of next year's budget and future strategic planning, which the subcommittee will be involved in. The subcommittee discussed the Ecological Modeling and Sustainable Chemistry sections. Dr. Klaper and Dr. Vorhees will add to these sections.

The subcommittee discussed adding sustainable chemistry to items for discussion for next year. They also discussed Dr. Stevens' work and hand curation of data, which is ecologically focused. Dr. Stevens stated reaction libraries could become a black hole of effort. Dr. Bahadori added that literature is poor and toxics researchers are trying to generate additional data. Dr. Williams is helping with web services and automation. Dr. Bahadori shared they are investigating conditions of likelihood of exposure. These are not computationally generated. She also stated that CSS is experimentally validating a reported transformation.

The subcommittee discussed persistent, bioaccumulative, and toxic transformation, and supported the goal of this area (i.e., what is the least environmentally impactful synthesis route). Dr. Bahadori stated that it is a mammoth effort given breadth of chemical space and number of chemical reactions in the space. CSS tries to focus on complex polymers. She acknowledged the need to annotate, curate, and encourage the program to merge reaction products from the bottom out and top down. Dr. Johnson inquired whether this was an area for a STAR grant and if the effort could be crowd sourced. Dr. Wiesner agreed that lifecycle high-throughput is a critical piece and supported the increased integration of sustainable chemistry into life cycle projects. Dr. Bahadori stated that, in absence of resources, CSS is repurposing and trying to make rapid progress. In the process, the program must slow down other efforts because of the lack of adequate resources. Dr. Johnson asked if there are other key gaps and areas for collaboration. He stated that there is a need to address cumulative exposures, which includes disposal and recycling and whether the "recycled" is in rapid exposure, but not in lifecycle context. He stated that some of data are really old, like CHADS.

The subcommittee discussed whether there are other gaps, such as LCA. For this section, the authors defined knowledge transfer and took feedback and sorted it into subcomponents. They added a recommendation that it would be helpful to hear more detail about how the collaboration worked. The subcommittee stated they would have liked to learn more about measures of success and most investigators could not answer this question when asked. Dr. Bahadori stated that this was a valid comment and was not presented because the meeting is too early in the project schedule.

Dr. Bahadori shared that the program to embed CSS scientists has been powerful. CSS gives it up out of pocket, which is a huge investment for two weeks of Title 42 scientists. Accomplishments include the design of the dashboard and push into private server.

Dr. McPartland shared her concerns about web-based tools and serious IT needs and challenges. After speaking with Dr. Richard Judson, she discovered that CSS is building modular and using open source code.

The subcommittee discussed stakeholder engagement and the impact of stakeholders from a poster, which showed that innovations document how other scientists are using tools. The subcommittee discussed the need to not just cite the published papers, but the actual tools (e.g., DOI for the model or the Open Researcher and Contributor ID [ORCID] number).

The subcommittee discussed the engagement of the National Institute of Environmental Health Sciences (NIEHS) and a focus on parts that the NIH is not getting funded, which could hold potential data sources to mine. This would be a good topic for a STAR grant.

The subcommittee shared a consensus that RFAs are not working well. The subcommittee noticed that CSS showed no evidence of engagement with non-governmental organizations (e.g., the Environmental Defense Fund and People for the Ethical Treatment of Animals). Dr. Bahadori stated that they do hold regular webinars. VTM webinars for academics are held biweekly. AOP webinars for stakeholders in the regions and states are also held biweekly. The subcommittee stated that evidence of this interaction and dissemination would be helpful (e.g., CSS has held 100 webinars). Dr. Bahadori shared that the Genius Bars are taken on 'road shows,' (e.g., demonstrations at SETAC meetings), which are usually mediated by NGO and stakeholder. She stated that that CSS will provide summary of statistics and the BOSC will cite these in their response.

Wrap Up and Adjourn
Ponisseril Somasundaran and Gina Solomon

Following the discussion of the draft write-up, the subcommittee discussed and agreed on a schedule for the path forward:

- **Monday, November 28**: Subgroups send final versions of their subsection text to Ms. Fleming for synthesizing into one document.
- **Wednesday, November 30:** Ms. Fleming will send the draft to Dr. Somasundaran and Dr. Solomon for review and smoothing into one voice.
- **Monday, December 5**: Dr. Somasundaran and Dr. Solomon will send the draft report back to Ms. Fleming, and she will distribute it to the full subcommittee for review and comment.
- **Friday, December 9:** Subcommittee members send their comments on the document to me (they could CC Dr. Somasundaran and Dr. Solomon, but do not send to the full subcommittee).
- **Monday, December 12:** Ms. Fleming will send the draft with all edits compiled to Dr. Somasundaran and Dr. Solomon, so they can reconcile edits.
- **Friday, December 16:** Draft final version of the report is sent back to Ms. Fleming for a fact check in coordination with CSS team.

- **Tuesday, December 20:** Ms. Fleming will send draft report back to Dr. Somasundaran and Dr. Solomon for final review.
- **Friday, December 23:** Dr. Somasundaran and Dr. Solomon will return the report to Ms. Fleming, and she will transmit it to the BOSC Executive Committee Chair.

The meeting was adjourned.

Appendix A: Agenda

United States Environmental Protection Agency
Board of Scientific Counselors (BOSC) Subcommittee for
Chemical Safety for Sustainability (CSS)

Meeting Agenda – November 16-18, 2016
EPA Campus, Research Triangle Park, North Carolina

Wednesday, November 16, 2016		
TIME	**Topic**	**Presenter**
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	Opening Remarks	Bob Kavlock, ORD Deputy Assistant Administrator for Science (by video)
9:15 – 9:30	Overview of Agenda, Organization of the Meeting, Discussion of Materials, and Highlights	Tina Bahadori, CSS National Program Director
9:30 – 9:45	Review and Discussion of Charge Questions	Ponisseril Somasundaran Gina Solomon
9:45 – 10:00	*Break*	
CSS Chemical Evaluation, Translation and Knowledge Delivery, and Complex Systems Science Topic Areas Research Project Deep Dives		
10:00 – 10:20	Adverse Outcome Pathway Discovery and Development	Dan Villeneuve/Steve Edwards
10:20 – 10:40	High-throughput Toxicology	Keith Houck/Tim Shafer
10:40 – 11:00	Rapid Exposure and Dosimetry	Kristin Isaacs /John Wambaugh
11:00 – 11:20	Demonstration and Evaluation	Richard Judson with Antony Williams
11:20 – 11:40	Virtual Tissues	Sid Hunter/Tom Knudsen
11:40 – 12:30	Subcommittee Discussion and Deliberation	Subcommittee
12:30 – 1:30	*Lunch*	
CSS Poster Session and Genius Bars		
1:30 – 4:30	Poster Session #1; Atrium B	CSS Scientists
1:30 -- 4:30	Concurrent Genius Bars; Classroom C113 SeqAPASS; AOP-wiki; ECOTOX DB; VT-LS	CSS Scientists
4:30 – 5:00	Subcommittee Discussion and Deliberation	Subcommittee
5:00 –5:45	Subcommittee Discussion of Charge Questions	Subcommittee Tina Bahadori
5:45 – 6:00	Wrap-up and Adjourn for the Day	Ponisseril Somasundaran Gina Solomon

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

Friday, November 18, 2016

TIME	Topic	Presenter
8:30 – 8:45	Welcome and Review of Day 1 and 2	Ponisseril Somasundaran Gina Solomon
8:45 – 9:15	Update on Human Health Risk Assessment (HHRA) National Research Program	John Vandenberg, HHRA NPD
Subcommittee Deliberations on CSS Charge Questions and Report Writing		
9:15 – 10:00	Subcommittee group discussion of CSS preliminary findings and recommendations	Subcommittee
10:00 – 12:00	Subcommittee breakout group by CSS charge questions -discussion and writing (includes a break)	Subcommittee Breakout Groups
12:00 – 1:00	*Lunch*	
1:00-3:00	Discussion of outstanding issues, review of draft report, review of timeline and assignment of follow up activities.	Subcommittee Breakout Group Leads
3:00 - 3:30	Wrap Up and Adjourn	Ponisseril Somasundaran Gina Solomon

Appendix B: Participants

BOSC CSS Subcommittee Members who attended:

Ponisseril Somasundran, *Chair*
Gina M. Solomon, *Vice-Chair*
Paloma Beamer
Chris Gennings
Dale Johnson
Rebecca Klaper
Jennifer McPartland
James Stevens
Donna Vorhees
Katrina Waters
Clifford Weisel
Mark R. Wiesner

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

EPA Presenters:

Tina Bahadori, *Chemical Safety for Sustainability, National Program Director*
Dan Villeneuve, *Office of Research and Development, National Health and Environmental Effects Research Laboratory*
Tim Shafer, *National Health and Environmental Effects Research Laboratory*
John Wambaugh, *National Center for Computational Toxicology*
Richard Judson, *National Center for Computational Toxicology*
Tom Knudsen, *National Center for Computational Toxicology*
Sid Hunter, *National Health and Environmental Effects Research Laboratory*
Caroline Stevens, *National Exposure Research Laboratory*
Todd Martin, *National Risk Management Research Laboratory*
Paul Price, *National Exposure Research Laboratory*
Kim Rogers, *National Exposure Research Laboratory*
Matt Etterson, *National Health and Environmental Effects Research Laboratory*
Carole Braverman, *Region 5 and the Great Lakes Restoration Initiative (by phone/webinar)*
Betsy Behl, *Office of Water, Office of Science and Technology*
Marie O'Shea, *Region 2*
Tala Henry, *Office of Chemical Sustainability and Pollution Prevention, Office of Pollution Prevention and Toxics*
Anna Lowit, *Office of Chemical Sustainability and Pollution Prevention, Office of Pesticide Programs*
Stan Barone, *Office of Chemical Sustainability and Pollution Prevention, Office of Science Coordination and Policy*
Bruce Duncan, *Region 10*
Kathleen Raffaele, *Office of Land and Emergency Management*

Wendy O'Brien, *Region 8*
John Vandenberg, *Human Health Risk Assessment, National Program Director*

Other EPA Attendees:

Barbara Abbott
Todor Antonijevic
Nancy Baker
Lenny Bankester
Jane Bare
David Belair
William Boyes
Robert Kavlock*
Daniel Chang
John Cowden
Kevin Crofton
Kathie Dionisio
Steve Edwards
Drew Ekman
Jill Franzosa
Christopher Grulke
Dale Hoff
Thomas Holdsworth
Keith Houck
Michael Hughes
Kristin Isaacs
Annie Jarabek
John Kenneke
Mitch Lasat
Jeremy Leonard
Ron Lernerd
Sylvana Li
Monica Linnenbrink
Michael Loughran
Annette Guiseppi-Elie
Todd Luxton
Myriam Medina-Vera
David Meyer
William Mundy
Tom Purucker
LyLy Pham
Katherine Phillips
Prachi Pradeep
Santhini Ramasamy
Kim Rogers
Katherine Saili
Seema Schappelle
Steve Simmons
Jon Sobus
Joseph Tietge
Daniel Vallero
Eric Watt
Barbara Wetmore
Antony Williams
Cynthia Wolf
Eva Wong
Douglas Young
Richard Zepp
Ben Zukowski
Todd Zurlinden

*Via teleconference

Contractor Support:

Canden Byrd, ICF
Catherine Smith, ICF
Sandra Chambers, ICF
Kim Osborn, ICF