# COMPUTATIONAL TOXICOLOGY SUBCOMMITTEE

**Face-to-Face Meeting Summary**
**Hilton Raleigh-Durham Airport at Research Triangle Park**
**4810 Page Creek Lane**
**Durham, NC**
**September 29 – 30, 2009**

## TUESDAY, SEPTEMBER 29, 2009

### Welcome and Introductions

*Dr. George Daston, The Procter & Gamble Company, Subcommittee Chair*

Dr. George Daston, Chair of the Board of Scientific Counselors (BOSC) Computational Toxicology Subcommittee, welcomed Subcommittee members and other participants to the fourth face-to-face meeting of the BOSC Computational Toxicology Subcommittee. The purpose of the meeting is to review the progress of the U.S. Environmental Protection Agency's (EPA) Computational Toxicology Research Program (CTRP) and make recommendations regarding the future of the Program. The Subcommittee members must be particularly vigilant as they make recommendations for the Agency in this critically important area. He asked the Subcommittee members to introduce themselves, including Dr. Lawrence Hunter who was attending via teleconference, and provide a brief description of their relevant experience. Following the introductions, Dr. Daston reviewed the meeting agenda. A list of the meeting participants and the meeting agenda are attached to this summary.

### Designated Federal Officer Remarks

*Ms. Lorelei Kowalski, EPA/Office of Research and Development (ORD), Subcommittee Designated Federal Officer (DFO)*

Ms. Lorelei Kowalski, Subcommittee DFO, reviewed the Federal Advisory Committee Act (FACA) procedures that are required for all BOSC Subcommittee meetings. The BOSC is a Federal Advisory Committee that provides independent, scientific peer review and advice to EPA's ORD and provides the opportunity for public comment. As the DFO for the Subcommittee, Ms. Kowalski serves as the liaison between the Subcommittee and ORD. It is her responsibility as the DFO to ensure that the Subcommittee's conference calls and meetings comply with all FACA rules. BOSC meetings are open to the public in accordance with FACA rules. All background information provided to the Subcommittee is available to the public on the BOSC Web Site. The minutes of the meeting are being taken by a contractor, Ms. Kristen LeBaron of The Scientific Consulting Group, Inc., and will be available on the BOSC Web Site after they have been certified by the Chair. Notice of this meeting was published in the *Federal Register*, and an electronic public docket was established. The electronic docket can be accessed at http://www.regulations.gov; the docket number is EPA-HQ-ORD-2009-0688.

To ensure that all ethics requirements were satisfied, each Subcommittee member has updated and signed the standard government confidentiality disclosure form. One conflict of interest was discovered with respect to one poster; therefore, the Subcommittee member will recuse himself from discussion of that poster.

This is the fourth face-to-face meeting of the Computational Toxicology Subcommittee; the previous face-to-face meeting took place in Research Triangle Park (RTP), North Carolina, in December 2007. The Subcommittee's draft letter from that review was discussed at the May 2008 BOSC Executive Committee meeting, and the final letter report was released in September 2008. ORD's response was presented at the February 2009 BOSC Executive Committee meeting. The three prior letter reports and ORD's responses have been provided to the Subcommittee members as an electronic copy with other pertinent meeting materials; all of these are available on the BOSC Web Site. Homework sheets and travel documents should be returned to Ms. Kowalski by the end of the meeting.

No requests for public comment have been received, but there will be time for public comment on Day 2 of the meeting at 12:00 noon.

## CTRP—Critical Component of EPA Science in the 21st Century

*Mr. Lek Kadeli, EPA/ORD, Acting Assistant Administrator*

Mr. Lek Kadeli thanked the Subcommittee members for their time and efforts in reviewing the Program and stated that the recommendations and engagement of the BOSC are appreciated. He explained that EPA Administrator Lisa Jackson is moving the Agency in a new direction with three guiding principles: (1) science must be the backbone for EPA programs, and EPA must be recognized as a premier scientific institution; (2) the Agency must adhere to the rule of law; (3) Agency actions must be transparent and collaborative.

Administrator Jackson encourages EPA collaborations to include constituencies and stakeholders to further improve the environment and protect public health. The Administrator also highlighted five priority areas for the Agency, which are to: (1) reduce greenhouse gas emissions, (2) improve air quality, (3) manage chemical risks, (4) clean up hazardous waste sites, and (5) protect America's waters. In terms of managing chemical risks, which is pertinent to the CTRP, more can be done to understand and implement steps to protect vulnerable populations.

ORD provides critical support for EPA's mission and addresses complex scientific issues that arise, such as increasing the pace of the dioxin assessment to conclude within the next year. ORD is redesigning the process of chemical assessments and producing high quality products in a timelier manner. Additionally, program and regional offices increasingly require ORD's expertise to solve their problems. Administrator Jackson's priority of managing chemical risks is important because evaluating the tens of thousands of chemicals present in the environment is a critical part of EPA's mission, and currently comprehensive data are available for very few chemicals of concern. To address this priority, ORD is building on newly available chemical, biological, and computational tools to transform the manner by which chemical exposure, hazard, and risk are evaluated. The overall goal is to deliver high-capacity decision-support tools to enable more efficient and effective assessment of chemical exposure, hazard, and risk. In moving forward, EPA has consulted with the National Academy of Sciences (NAS) and National Research Council (NRC) regarding toxicity testing and cumulative risk assessment. The NAS introduced a conceptual framework in its 2007 report *Toxicity Testing in the 21st Century: A Vision and a Strategy* that describes how to test more effectively to identify exposure pathways and actual risks and provide decision-makers information to mitigate and address risk.

EPA's 2009 Strategic Plan was developed with partners to ensure that the right strategic goals were established. Some of the strategic goals include toxicity pathway identification and screening, pathway-based risk assessment, and institutional transition. ORD has approached the challenge by asking how it can best address issues with high-quality work and nimbleness. The National Computational Toxicology Center (NCCT) was created to address such problems, develop creative solutions, and work broadly across ORD and externally.

Dr. Daston commented that the strategic plan was developed by the Agency, but the NCCT has a good deal of ownership as well. The Center is recognized as visionary by various stakeholders. He also noted that the NRC is assessing the value of Title 42 positions, which have allowed talented scientists to engage in problems that EPA and other federal agencies address. Mr. Kadeli confirmed that ORD has effectively used its Title 42 positions to improve its programs. He stated that ORD is engaging the NRC on this issue because Title 42 is an important mechanism to attract scientists to address gaps and challenges and allows the Agency to compete with academia, industry, and other federal agencies for the top scientists.

**CTRP Overview: Informatics, Chemical Prioritization, and Systems Biology**
*Dr. Robert Kavlock, EPA/ORD, NCCT Director*

Dr. Robert Kavlock provided a high-level overview of the Program; he explained that the posters will provide the specific scientific details and metrics. The current approach for toxicity testing is expensive (approximately $11 million per chemical) and lengthy (taking years to complete). Neither the regulated industry nor the Agency cannot afford to spend this amount of money or time on the 9,912 chemicals in which it is interested. As a consequence, the Agency has little to no chronic toxicity data on more than 70 percent of these chemicals. The mission of the Computational Toxicology within the Agency is to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessments of chemicals and therefore provide decision-support tools for high-throughput screening and risk assessment and management.

Predicting human toxicity is a significant challenge because it has to examine chemical interactions at the multiple levels of biological complexity, from molecular targets, to cells and ultimately cellular networks that collectively determine manifestations of toxicity. The National Research Council recently proposed a transformation in the conduct of toxicity evaluations that were based on four main principles: (1) provide the broadest coverage of chemicals, endpoints, and life stages; (2) use the fewest animals with the least suffering per animal; (3) cost the least amount in the least amount of time; and (4) provide detailed mechanistic and dose information for human health risk assessment. Accomplishing any one is difficult, so meeting all four objectives when prioritizing is a significant challenge. The CTRP effort is highly consistent with the NRC vision as it employs biochemical and cell-based high-throughput screening (HTS), complex cellular high-content and HTS, model organism medium-throughput screening, virtual tissues, and the Toxicity Reference Database (ToxRefDB) as methods of toxicity investigation.

Dr. Kavlock noted several key points relative to the CTRP, such as ORD's mission to lead the translation of scientific advances to protect human health and the environment, program office recognition that current chemical risk assessment methods are insufficient, research advances in biology and computer science are enabling a transformation in the field of toxicology, and the international recognition that computational toxicology is the leading edge of change. The CTRP is tackling a nationally and internationally important problem, and EPA is the only federal agency that employs staff with unique expertise in biological science, computational models, and information technology who are dedicated to risk assessment. The CTRP has a commitment to transparency and the public release of all data. Dr. Kavlock highlighted the charge questions for the current BOSC review and some of the recommendations from the prior review.

The CTRP is comprised of the NCCT, the NCEA funded Science To Achieve Results (STAR) research centers, and additional ORD input. The CTRP 2009 budget includes 34 full-time equivalents (FTEs) and $15 million. The NCCT receives 22 of these FTEs and $7.5 million. ORD input includes seven "new start" projects that began in 2004, with newer activities involving collaborations with the National Exposure Research Laboratory (NERL) and the National Health and Environmental Effects Research Laboratory (NHEERL). The CTRP has developed its second-generation implementation plan, which has been internally reviewed by EPA and which has been provided to the BOSC for their input on the plan as well. The second implementation plan combines the three original Long-Term Goals (LTGs) into one comprehensive LTG, expands beyond hazard prioritization, supports EPA's Strategic Plan for Evaluating

the Toxicity of Chemicals and anticipates ORD's integrated multidisciplinary program on improving chemical risk management. The plan proposes decreased the emphasis on physiologically based pharmacokinetic (PBPK) models and chemical-specific efforts as these are covered by other components of ORD

The Program has evolved to include four STAR centers, ToxCast™ Phases I and II, and several databases (e.g., ToxRefDB). Another Request for Applications (RFA) will be issued in Fiscal Year (FY) 2010 to create a fifth STAR center. The NCCT leverages its efforts via establishment of many partnerships that include Material Transfer Agreements, Memoranda of Understanding, Cooperative Research and Development Agreements, and Interagency Agreements; these are detailed in tbe briefing materials provided to the BOSC. In March 2009, the NCCT entered a landmark agreement with Pfizer, Inc., which will provide chemical and toxicity data on pharmaceuticals that failed because of human toxicity. Significantly, all results will be made public.

Dr. Kavlock provided an overview of Program mentoring and staffing since 2007, which includes the mentorship of six predoctoral students, 16 postdoctoral fellows, and three Computational Toxicology Rotational Fellows. The Program currently is recruiting four postdoctoral positions and a communications specialist. The Computational Toxicology Rotational Fellowship Program was launched in April 2008, in an effort to train Agency personnel in computational toxicology so that they can return to their offices, centers, or laboratories with unique skills, knowledge, and tools. Additionally, CTRP staff members serve on numerous journal editorial boards, federal and international agency review panels, workshop organizing committees, and EPA working groups.

The Program co-hosted a workshop on virtual tissues with the European Union and hosted a ToxCast™ data workshop in RTP with 200 attendees from 14 countries. The Center publishes approximately 30 peer-reviewed papers each year, and the Web site receives 10,000 to 12,000 unique hits per month. Current management priorities of the Program include developing toxicity predictions and chemical prioritizations that incorporate exposure, strengthening cross-ORD collaborations, participating in the Tox21 collaboration between the Agency and the National Institutes of Health (NIH), communicating computational toxicology, and developing clients for virtual tissues.

Dr. Dennis Paustenbach asked how many FTEs and how much funding the Program received. Dr. Kavlock responded that the Program received 34 FTEs, some of which are assigned to overhead and laboratories. The NCCT receives 22 FTEs, two of which are administrative. The current research budget is $15 million, 50 percent of which funds the NCCT; the STAR centers and ORD projects each receive 25 percent of the budget. The FY10 budget is approximately $20 million.

Dr. John Quackenbush asked how many principal investigators lead projects. Dr. Kavlock responded that this was a complex question because there are nine major projects on which each of the project teams must work together. Generally, one senior staff member leads a project with one or more assistants.

Dr. Cynthia Stokes asked, in terms of transparency and the public release of data, what was being released with respect to models, algorithms, and databases. Dr. Kavlock responded that all of these are publicly available; the CTRP has developed user-friendly interfaces to make the information more accessible. He mentioned that these will be demonstrated during the poster sessions.

Dr. Ali Faqi noted that this is a complex program with multiple STAR centers and asked whether there was overlap in the work conducted by the centers. Dr. Kavlock responded that the work performed by the centers is complementary. There is a significant amount of coordination when projects are designed. Projects also are coordinated across the Federal Government via the Tox21 collaboration.

Dr. M. Moiz Mumtaz asked Dr. Kavlock to comment on the method for determining tissue dose from cellular system information. Dr. Kavlock explained that the research will focus on external exposures and

how to develop prioritization tools, exposure science, or HTS based on what others have accomplished; the Program will rely on NERL and NHEERL for PBPK expertise to help with this endeavor.

**Introduction to Poster Session I: Informatics, Exposure Science, and ORD and External Partners**
*Dr. Ann Richard, EPA/ORD/NCCT*

Dr. Ann Richard provided an overview of the 19 posters included in Poster Session I, which broadly encompasses informatics, exposure science, and ORD and external partners. The posters are divided into two themes—models and data foundations. Five posters focus on informatics, four each on systems modeling approaches and exposure science, and one on HTS; five posters focusing on STAR center research touch on all of these areas. Dr. Richard presented the central concept of each of the 19 posters to help each Subcommittee member determine which posters required his/her expertise; each of the Subcommittee members chose three or four posters on which to concentrate during the poster session, ensuring that each of the posters was assigned to at least one Subcommittee member.

**Poster Session I**

This poster session was held in the Rose Room. The Subcommittee reviewed 19 posters in this session. During the 120-minute poster session, each Subcommittee member had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to the Subcommittee members prior to the meeting.

**Poster Session I: Discussion**
*BOSC Computational Toxicology Subcommittee*

Dr. Daston explained that the posters provide scientific details that represent what the Program is trying to accomplish so that the Subcommittee can make strategic-level recommendations. Overall, he was impressed, particularly with an Agency project initiated outside of NCCT that has made a good deal of progress. It is a nice model for how the Program has leveraged resources and taken advantage of Agency expertise.

Dr. Quackenbush focused on the informatics posters, and he was impressed with the amount of work that has been performed. Currently, there are millions of dollars worth of data that are stored in an incompatible manner with no easy method to link all of the data together. The focus has been the development of various tools that attempt different methods of data organization. Each tool has been developed independently, but as they evolve, the links between the tools increase, which eventually will allow people to mine the data. Although the progress still is in the aggregation stage, the long-term plans will allow synthesis and analysis. This is a good start, but it is important to recognize that this endeavor will not be easy or inexpensive. The CTRP is building useful and useable tools, but achieving the ultimate goal will take some time. It will be beneficial to see these projects grow and mature.

Dr. James Clark examined the posters dealing with Tox21 and STAR to help him answer the charge question he was assigned. The Program has improved, evolved, and built true partnerships. The STAR centers have added new perspectives, approaches, and ideas without competing with the CTRP and NCCT. There is a good deal of synergy and many accomplishments. The international collaborations are admirable, particularly considering that the funds are constrained to be used nationally only. Dr. Daston agreed that it was impressive how the STAR centers complement the internal research.

Dr. Stokes supported the comments on the STAR centers and noted that some posters (e.g., 14 and 17) dealt with very specific problems. In examining such specific issues, the researchers must consider whether they are gathering the right data, examining the right details, and performing the right assays to allow the research to translate to broader issues. This is a common problem throughout toxicology and

biology. How a specific test ultimately may be used for decision-making must be considered. The literature is filled with examples of experiments that are not truly related. Regarding the asthma project, Dr. Stokes said she liked the approach of examining how exposure relates to biology; this is an important study that could set the standard for working on other disease areas.

Dr. Santiago Schnell thought that the approach to setting up the STAR centers was wise, and these centers are performing good work. He had some concerns about taking known toxins to determine toxicity (resemblance modeling) and moving to predictive modeling because this will take a good deal of time, and the centers' grants are close to completion with no mechanism for renewal. Therefore, this research could be lost. He reminded the Subcommittee members that it takes 5 to 10 years to make sensible predictions. To be successful, it is important to consider how the centers will accomplish this within the constraints placed on them.

Dr. Richard Di Giulio examined the posters in terms of the charge question he was assigned, which deals with how the NCCT is contributing to the advancement of toxicology. The posters he reviewed certainly give evidence that the NCCT is making contributions. He was impressed with the poster on a project that explored the continuum from mechanistic events through cellular outcome all the way to the population level. He also was impressed with the asthma project. This work appears to be some of the best at linking outcomes at the human, population, and ecosystem levels to modern techniques.

Dr. Faqi commented that the *in vivo* testing adds an advantage in understanding the mechanisms of toxicological testing and pathways. The Program is exciting and moving in the right direction. Every poster described a different method to bring clarity to a complex issue.

Dr. Paustenbach noted that the old mindset has changed, and this Program is focused on how to take the knowledge gained and apply it to understanding thousands of chemicals. The posters he saw today make it clear that the CTRP is making strides toward assembling and integrating a large amount of data. Toxicology has been very inefficient during the past 25 years, and one possible outcome of the CTRP's work is that the efficiency of toxicity testing will increase dramatically. He noted that not all associations are causal, and this determination must be made. He cautioned against mining the database too early.

Dr. Mumtaz noted that an ongoing struggle has been linking exposure and toxicity, and some posters described projects aimed at tackling this. Comparative toxicology at the subcellular, cellular, and whole animal levels is a challenge; it is difficult to determine what circulates throughout the body versus what is taken up in a cell. He suggested that projects be initiated to investigate more closely exposures to chemical mixtures.

Dr. Katrina Waters agreed with Dr. Stokes' concern regarding the specificity of some of the projects. The posters that she examined described projects that use specific systems to identify toxicity pathways; determining the relevant assays that could be developed in a systems platform would greatly enhance the power of the database to discriminate among chemicals and chemical classes. Additionally, many of the approaches were focused on known systems, and although genomics and proteomics are being employed, the researchers are not looking at the bigger picture. Therefore, Dr. Waters encouraged the computational personnel to take an unsupervised approach to exploring the data to determine what else is present and broaden the output.

Dr. Hunter acknowledged that he had not had the chance to speak with the poster presenters, which probably would have answered his questions, but he had modest concerns about how well the work connects with research external to EPA. Certain methodologies or computational tools have been adopted, and he did not understand the rationale for the selection. He suggested that the Program consider alternative methodologies and tools and how to evaluate them in accomplishing its goals.

## Comments on the CTRP

*Dr. Peter Preuss, EPA/ORD, NCEA Director*

Dr. Peter Preuss provided a presentation on transforming toxicology and implications for human health risk assessment. Human health risk assessment still is fundamental to EPA's approach for analyzing potential risk from exposure to environmental pollutants and is a key piece of information for regulatory decision-making. Human health risk assessment is constantly evolving with new scientific developments, greater scientific understandings, and new technologies. The current challenge, as it has been for many years, is to address emerging science and its related issues. Because of the kind of information available today, the current approach to risk assessment is unwieldy, time consuming, and expensive, with few epidemiology studies that can be utilized. He reiterated the earlier points that there are tens of thousands of untested chemicals, and current toxicology methods are too expensive and slow. As a result, toxicology approaches are moving away from *in vivo* testing. Innovative approaches must be developed to deal with greater numbers of chemicals in a cost-efficient, timely manner.

Risk assessment approaches are being discussed that can use the new data types and arrays that are being developed within the CTRP, and ORD's Human Health Risk Assessment Program (HHRAP) and CTRP are in close partnership to move human health risk assessment forward and develop the next generation of risk assessment. The future approach will provide more information about increased numbers of chemicals, but these data will be different from previous generations of data. Therefore, it is necessary to determine how to use the data effectively and appropriately. Recognizing that risk assessment data needs cannot be met with current testing methodologies, EPA consulted with the NAS on the future of human health risk assessment and received a series of recommendations that will define the Agency's path forward. In addition to the challenges that NAS identified, there are a number of other issues that must be addressed, such as identifying techniques and knowledge to improve throughput approaches and thinking differently about risk assessment. HHRAP and CTRP are collaborating to address these issues. One recommendation was to examine chemicals for cumulative effects that act to result in similar health endpoints rather than look similar chemically; this new approach is being applied in a series of case studies.

ORD is exploring new science, methods, and policies that can be incorporated into emerging and future risk assessments. The approach is to develop prototype next-generation risk assessments, examine them, learn from them, modify them, and then refine the next versions based on the new knowledge. HHRAP and CTRP are learning from each other and becoming familiar with human health risk assessment approaches and computational toxicology methodologies to develop case studies to explore the use of computational toxicology data in human health risk assessments using a combination of traditional and computational toxicology data. NCEA considers NCCT research to be the "wave of the future," for risk assessment and EPA is building a risk assessment program that will be centered on CTRP's research products.

*Mr. Jim Jones, EPA/Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Deputy Administrator*

Mr. Jim Jones explained that OPPTS is one of CTRP's EPA clients. OPPTS makes thousands of regulatory decisions annually about pesticides and industrial chemicals and these decisions must be timely. For a vast majority of the 9,000 chemicals in the National Industrial Chemical Program there is little or no data. Innovative methods to assess chemicals are needed to accomplish the task of evaluating all of these chemicals. OPPTS is transitioning toward new integrative and predictive 21st century techniques to better characterize risk and increase the efficiency and effectiveness of testing and assessment. To accomplish this, collaboration is needed at all stages (i.e., research, method development, evaluation, review, and regulatory acceptance) so that the products are useful and relevant. OPPTS

communicates with NCCT at each step to help ensure this. The collaboration uses critical path parallels and partnerships between programmatic and research activities to align the work so that it is responsive; this provides the basis to work with stakeholders and use the science to evolve the program.

OPPTS and the CTRP have collaborated on both phases of ToxCast™, ToxRefDB, the Distributed Structure-Searchable Toxicity (DSSTox) Database Network, and cumulative risk. CTRP research findings have been incorporated into assessments, illustrating their useful applications. In the short to medium term, OPPTS can use the ToxCast™ tool for priority setting, evaluating and strengthening chemical categories and clusters, and developing a new generation of quantitative structure-activity relationships and expert systems. In the medium to long term, ToxCast™ can provide a sound scientific foundation to inform decision-making. ToxCast™ also is a tool for use by the Endocrine Disruptor Screening Program (EDSP) to prioritize chemicals, fill data gaps, predict *in vivo* endocrine effects, and identify additional studies or uncertainty factors. Additionally, external partnerships and stakeholder engagement are important to include in the tools-development process so that support is in place.

Mr. Jones concluded that CTRP research is valuable, and OPPTS is extremely interested in continuing to work with the Program and NCCT to develop relevant and useful computational toxicology tools than can be applied in short-, intermediate-, and long-term regulatory contexts. To move forward, existing CTRP collaborations with national and international agencies, academia, and the scientific community should be continued and expanded, engaging clients and stakeholders from development to implementation of tools that address ecological and human health risks.

### *Dr. John Bucher, NIH/National Institute of Environmental Health Sciences, National Toxicology Program Associate Director*

Dr. John Bucher explained that the Tox21 community has a vested interest in the CTRP process and wants the Center to succeed. Initially, ToxCast™ was an experiment whose technical feasibility, sensitivity, specificity, and ability to produce useful and coherent findings were unknown. The methods that EPA used to move forward were visionary, including contracting commercial high-throughput assays, using registered pesticide actives, collaborating with the National Toxicology Program and NIH Chemical Genomics Center, effectively communicating with stakeholders, and developing remarkable databases. ToxCast™ was found to be technically feasible and able to produce useful and coherent findings. The toxicity pathway universe is complex, and modes of action are a current "black box." It is unknown whether these pathways provide key events in mode of action, underlie the various pathologies and altered physiology that reflect modes of action, or allow, enhance, or supersede cross-species extrapolation. Conceptual validation, human risk assessment and hazard identification, priority setting, and the ability to apply a "generally recognized as safe" label to appropriate chemicals will be required for acceptance of toxicology in the 21st century. The toxicology community must not lose sight of the fact that assays provide intrinsic knowledge in and of themselves. Mr. Bucher's perspective is that the CTRP is successful, productive, innovative, cooperative, publicly accessible, well managed, timely, and addresses the right questions. The Tox21 community is working toward a common goal, and he has never seen a group work so well together.

### *Dr. Cal Baier-Anderson, Environmental Defense Fund*

Dr. Cal Baier-Anderson presented information from a nongovernmental organization (NGO) perspective. There are policy issues that need to be addressed, and computational toxicology may be able to help by addressing the huge legacy of unassessed chemicals, addressing emerging endpoints and science, identifying intrinsically safer chemicals, and ensuring the safety of complex emerging technologies. NGOs are concerned that there is insufficient attention being paid to pathways leading to chronic diseases (e.g., autism) and emerging endpoints and science, which need to be integrated into a computational toxicology framework. Currently, the basis for assay validation is too limited, and assay interpretation is a "black box." NGO priorities include the following questions: How will risks to sensitive

subpopulations and life stages be characterized? Is *in vitro* dose-response *in vivo* relevant? What is a significant perturbation?

To be relevant to public health concerns, computational toxicology must incorporate concerns such as increasing rates of chronic disease. Pathways and endpoints must capture disease pathways, and testing must be targeted to protect sensitive and susceptible populations. Environmental exposures must be regarded as a component of multifactorial causes. There are many emerging science and complex endpoints that computational toxicology must integrate within the fields of epigenetics, neurotoxicity, and immunotoxicity, and EPA needs to engage scientists in these fields and utilize NGO expertise in assay development and interpretation to reduce the current levels of skepticism. NGOs also are concerned that the current approach of ToxCast™ integrates *in vivo* and *in vitro* data in such a manner that similar endpoints are not being compared. The recommendation is to compare *in vivo* and *in vitro* assays that cover the same endpoints, which is especially important for complex pathways. NGOs want the HTS results for endocrine disruptors to be compared with in *vivo* bioassays and the EDSP test battery. Additionally, when interpreting data, it is necessary to account for risks to sensitive subpopulations and each life stage, recognize that perturbation occurs along a continuum, and consider the *in vivo* relevance of dose-response. NGOs recommend that EPA institute a dialogue with stakeholders that leads to guidance on interpretation of results.

There are new opportunities to think beyond traditional risk assessment applications, advance green chemistry by providing additional data for informed substitution or identifying chemicals with lower biological perturbation profiles, and address the mixtures challenge. Continued funding of NCCT will help advance alternative testing methods and analysis. Resources also are needed to foster a dialogue on the interpretation of assays for decision-making. For maximum benefit, NCCT should collaborate with Agency experts in the Pollution Prevention, Green Chemistry, and Design for the Environment Programs.

Dr. Daston asked for a list of possible scientists to include in future panels, and Dr. Baier-Anderson promised to provide such a list. Dr. Di Giulio asked why cancer was not included in the list of chronic diseases. Dr. Baier-Anderson responded that the focus was on emerging chronic diseases.

Dr. Hunter asked Dr. Kavlock whether NCCT collaborates with the Green Chemistry Program. Dr. Kavlock replied that the Center has engaged in dialogue with the Green Chemistry and Design for the Environment Programs. He noted that the "Father of Green Chemistry" likely will be the next ORD Assistant Administrator, so there probably will be an increased focus on green chemistry.

Dr. Daston thanked the presenters for their comments and recessed the meeting at 6:14 p.m.

## WEDNESDAY, SEPTEMBER 30, 2009

Dr. Daston reconvened the meeting at 8:49 a.m. and provided an overview of the day's agenda.

### Introduction to Poster Session II: Toxicity Pathways Supporting Chemical Prioritization and Systems Models

*Dr. Tom Knudsen, EPA/ORD/NCCT*

Dr. Tom Knudsen provided an overview of the 16 posters from Poster Session II, which focus on the topics of HTS data, toxicity predictions, virtual tissues, and uncertainty analysis. Key questions to consider during the poster session are: (1) What are the fundamental cellular targets of environmental chemicals? (2) Can predictive signatures of toxicity be unlocked from the HTS data? (3) Why endeavor to conquer the *in silico* reconstruction of tissues? (4) How does parameter and model uncertainty scale to a systems-level? Dr. Knudsen provided a brief overview of HTS, toxicity predictions, hazard-based prioritization, virtual tissues for systems modeling, and uncertainty analysis to provide background for the posters highlighted in this session. He presented the central concept of each of the 16 posters to help the

Subcommittee members determine the expertise required to review each poster. Each Subcommittee member chose three or four posters on which to concentrate during the poster session, ensuring that each of the posters was assigned to at least one member.

**Poster Session II**

This poster session was held in the Rose Room. The Subcommittee reviewed 16 posters in this session. During the 120-minute poster session, each Subcommittee member had the opportunity to ask questions about the research or clarify specific points with the presenter(s). Poster abstracts and a book of poster reproductions were provided to Subcommittee members before the meeting.

**Poster Session II: Discussion**
*BOSC Computational Toxicology Subcommittee*

Dr. Quackenbush stated that the key driver of successful engineering, the focus of the posters he examined the previous day, is having science that motivates and guides the building of the infrastructure. Today he was able to examine applications that build on that infrastructure. He was impressed with the number of applications that are helping leverage what has been done previously and providing guidance for how that should move forward. He also commended the Program for its training component; the postdoctoral fellows were bright and motivated, and this component will help move this program and the Agency into the future.

Dr. Clark commented that the ToxCast™ effort represents the Center's progression as a result of deliberate planning. It is rewarding to see the Program yield results and launch Phase II of ToxCast™, an innovative project that will move the Center forward. The CTRP has matured and the tools are easily linked to the research. Dr. Daston agreed that there is a good deal of value added from ToxCast™, which started as a predictive exercise, and a large amount of ToxCast™ data is being used throughout the Program.

Dr. Paustenbach asked if the Agency would call for scientific forcing of a number of chemicals that would make the regulatory community or entities that benefit from producing the chemicals responsible for performing classical experimentation. Dr. Daston responded that one of the visions is to perform more informed toxicity testing.

Dr. Faqi found it very interesting to move from ToxCast™ data to HTS to virtual tissues and toxicity predictions. He hopes that the predictive models will be user-friendly for all toxicologists.

Dr. Stokes spent time exploring virtual tissues and ToxCast™, particularly the Virtual Liver Program (v-Liver™). The project was in its infancy at the time of the last BOSC review, and the Subcommittee encouraged the Program to keep its grand vision but be practical in performing small steps to show a reasonable amount of progress. The Program has accomplished this by focusing carefully on short- and long-term staging. Specific outcomes that are of concern to the toxicology community also have been a focus. The CTRP is adept at choosing chemicals relevant to the Agency's mission. Dr. Stokes recommended that as the Program gathers data and builds mathematical and simulation models that it chooses very specific data to calibrate and verify against known data so that confidence in the model is increased. To create a testable product, the model must be produced so that the results can be measured and verified. It is important to have the ability to work with all kinds of experimentalists so that all types of data can be gathered; this type of integration appears to be occurring. Chronic versus acute exposures and animal versus human data must be considered.

Dr. Daston was impressed with the degree of collaboration and amount of leveraging that the Program has accomplished. Dr. Schnell agreed, stating that he was impressed with how EPA has fostered successful collaborations, and he encouraged the Program to continue such collaborations. Dr. Waters applauded the

CTRP for stepping to the forefront to test the Tox21 paradigm. The next challenge will be to apply lessons learned to move from Phase I to Phase II of ToxCast™. She saw inconsistencies between what the experimentalists and the mathematicians considered predictive, so she encouraged the Program to keep the statisticians involved in the evaluation.

Dr. Di Giulio was impressed with the progress achieved since the previous BOSC review. He had been skeptical about the virtual tissues projects, but now he thinks that have real potential. Dr. Mumtaz agreed with Dr. Di Giulio's previous and current assessments of the virtual tissues projects. He suggested that the experimentalists, modelers, and risk assessors collaborate at the beginning of each project and perform community outreach so that the model and output are relevant, and the community is satisfied. NCCT must involve other program offices; some cross-talk is taking place, but clients need to know what is occurring so that the research and products are useful. Most of the concerns that he had prior to the meeting, were alleviated in the poster session. The mentoring is positive, and he is impressed with the Program.

Dr. Hunter wondered whether there was a metaphorical equivalent to the translational medicine work that NIH is promoting that integrates basic science with direct applications. There is an opportunity to ensure that the basic science links directly to other research areas that meet the needs of decision-makers, although there does not seem to be a specific focus on this despite research that exists that can help foster these linkages. He recommended that the Program explore user-centered designs, the kind of research that evaluates in a formal scientific manner what the end users need. This will allow priorities to be set. There is a clear desire within the CTRP to serve its customers, but there is less of a scientific focus on how these customers can be served.

Dr. Daston thanked the poster presenters from each session for their enthusiasm and the extensive work they did on their posters.

### CTRP Future: Providing High-Throughput Decision-Support Tools for Screening and Assessing Chemical Exposure, Hazard, and Risk

*Dr. David Dix, EPA/ORD, NCCT Acting Deputy Director*

Dr. David Dix thanked the Subcommittee members for their valuable input regarding the Program. The future of toxicity testing has been defined by several publications in the literature by the NAS, the NIH Director, and others. Putting all of these publications together in context provides the pathway for the future of targeted risk assessments. The CTRP second-generation implementation plan expands beyond hazard prioritization, supports EPA's Strategic Plan for Evaluating the Toxicity of Chemicals, and anticipates ORD's integrated multidisciplinary research on improving chemical risk management expected to be introduced in FY11. Future chemical prioritizations will involve synthesized analysis of data to predict outcomes for subsequent prioritizations. The current CTRP projects will combine to provide a more complete set of analyses for the potentials for hazard, exposure, toxicity, and human disease that will feed into a process to identify toxicity pathways and related human disease outcomes.

Incorporating metabolism and dosimetry into HTS and predictive modeling is important, and collaborations with NERL and NHEERL will be the key to success. Collaborative efforts also will be critcal to predictive biotransformation. NCCT is working closely with NERL on ExpoCast™ to develop databases, models, and tools that are required to understand the "exposome" for environmental chemicals. Various internal and external partners are working together to expand biological domains and HTS assays feeding into predictive toxicology modeling efforts. NHEERL collaborations will allow the comparison of *in vivo* and *in vitro* results in an iterative fashion, especially for the virtual tissues projects. An FY10 RFA for an additional STAR center will address issues related to hazard, exposure, dosimetry, effects, and life-stage susceptibility via virtual tissues. Virtual tissues allow a systems-level approach that moves beyond empirical models to systems models, which eventually will support next-generation risk

assessments. A tiered approach to risk assessments is being developed with NCEA, including the integration of HTS and other data from the CTRP into these next-generation risk assessments.

CTRP databases will provide a foundation for predictive/systems toxicology, and transparency is important for widespread use and utility. Many of the databases are used by the public online, and others are expected to be published by the end of 2009. Literature mining and knowledge discovery knowledgebases will also be made wholly available. Public availability and communication to stakeholders makes the research progress transparent, and Tox21 and other communities are important for supporting the strategic plan. ToxCast™ is being expanded to directly link to EPA programmatic needs. In the future, the Office of Pesticide Programs plans to use ToxCast™ to provide a strategic direction for new pesticide testing and assessment approaches, and ToxCast™ assays will also support the EDSP, a major program within the Agency. CTRP is developing methods to understand data and apply this knowledge to meet the needs of various programs and offices across EPA, including the Design for the Environment and Nanoscale Materials Stewardship Programs, and the Office of Water. Over the coming years, screening and prioritization will level off as complete datasets are established, and efforts will focus more on pathway based risk assessments. This will require institutional transition across the Agency. On September 29, 2009, Administrator Jackson announced essential principles for the reform of chemicals management legislation, as well as an initial list of chemicals that EPA is considering for action plan development. The first action plans are to be developed during the next few months and will require a significant amount of effort. CTRP is equipped to provide informatics and prioritization tools to contribute to types of activities in the future.

Dr. Di Giulio noted that there appears to be a move toward a human health focus rather than an ecological focus. Dr. Dix agreed, explaining that this focus was important during the first five years of the Program, but that as necessary HTS tools come available they will support expansion to examine ecological issues. Similarly, the OECD Molecular Screening project that the CTRP supports is also focused on human health but moving toward ecological issues as well. Knowledge and experience can be transferred between human health and ecology within the Program, and this will be taken advantage of. Dr. Daston added that the green chemistry area on which the CTRP is focusing expands beyond human health; environmental factors must be considered in green chemistry, and the CTRP can contribute to this.

Dr. Hunter noted that there is a swift and increasing dependence on computational tools and databases. He has concerns about the software engineering process because errors could have a profound effect on outcomes. How is the Program ensuring that the rapidly developed software meets quality assurance standards? Dr. Dix replied that EPA has a mature quality assurance program, and all tools and models developed within ORD meet these stringent quality standards. Stakeholders also review the software or database content for quality assurance and control. Dr. Hunter asked how many and what types of errors were found in the ToxRefDB database. Dr. Dix responded that the error rate was much lower than 1 percent and involved lack of clarity in the nomenclature and vocabulary regarding toxicity endpoints. Dr. Richard Judson added that there is a careful process in place to ensure that the correct testing is performed regarding chemical assay data. There is a process to ensure that data are quality controlled using past knowledge and replicate chemicals to characterize the amount of uncertainty. Off-the-shelf techniques are used in informatics to understand how well the data have been captured. The iterative process that is in place checks results two to three times. Dr. Hunter commented that errors in scientific software are not unusual, and he was concerned that the software engineering practices be at the same high-quality level as data production practices. He added that the Program should consider software testing, and Dr. Judson agreed to give that consideration. Dr. Quackenbush added that open-source projects will ensure that the broader community can assess the software.

Dr. Faqi asked whether the CTRP was going to expand its virtual tissues projects to other tissues. Dr. Dix responded that the Program would like to collaborate with or facilitate such an effort by partnering, but it cannot make internal commitments at this point. The liver was chosen as a priority because of its importance to toxicity as a primary target organ, and the embryo was chosen because it is a unique model

system for a highly critical life stage. Dr. Kavlock added that Dr. Peter Hunter of the University of Auckland in New Zealand is working on a virtual heart, and NHEERL is developing a cardiopulmonary virtual system, but the CTRP does not have the resources to pursue other virtual tissues at this time.

Dr. Quackenbush asked Program leaders to discuss the role of STAR centers during the next 3 years. Dr. Kavlock replied that the newest STAR center will greatly assist the virtual embryo (v-Embryo™) effort, and the FY10 RFA for a fifth STAR center will support the v-Liver™ effort. Unfortunately, there is no renewal mechanism for the other STAR centers. Dr. Quackenbush commented that the extramural component provides significant value in a number of areas.

## Public Comment Period

Ms. Kowalski called for public comment at 12:00 noon. No comments were offered.

## Working Lunch

During a working lunch on Wednesday afternoon, the Subcommittee members continued to discuss their strategy for completing their draft report.

## Subcommittee Working Time

*BOSC Computational Toxicology Subcommittee*

Dr. Daston stated that before leaving the meeting, the Subcommittee must have a plan to address each charge question. The draft responses to the charge questions should be sent to Ms. Kowalski within 10 days following the meeting so that a draft report can be assembled and sent to the Subcommittee members for review before the discussion during the October 21, 2009, teleconference. The purpose of the teleconference will be to finalize the draft report. Sending the responses to the draft charge questions by October 10, 2009, will allow 10 days for the other members to add comments, suggestions, and examples to the charge question responses to which they were not assigned. He reminded the members that the focus should be strategic, and points should be illustrated with specific examples. Dr. Daston went over each charge question briefly to solicit Subcommittee members' opinions about the responses to each question.

The general thoughts in terms of Charge Question 1 were that the CTRP has produced tools that fit into EPA's mission, but the Subcommittee was not aware of any Agency decisions that have been supported by the tools. The Program has faced complexities, such as the common problem of data not being as systematically described as possible, but has not reached the stage in which data are systematically linked; the Program recognizes this, however, and is moving forward. The infrastructure is in place, and the various pieces are coming together, but the connections to risk assessment are nebulous. NHEERL PBPK experts can be used to help Program scientists think about how to use uncertainty analysis in risk assessments. Statisticians also need to be involved when moving forward. It must be recognized that "high quality" and "high quantity" are mutually exclusive, and a molecular approach will not produce data of the same quality as other approaches. The research focus of the Program is appropriate, but major results and the ability to provide more data are needed. Predictions must be quantitative, and it still is unknown whether the Program can provide hazard identification. The Subcommittee members acknowledged the tremendous amount of outreach from the Center to the project offices. The approaches that the Center is using to accomplish its goals were discussed and found to be appropriate. The verbiage used on Slide 4 of the PowerPoint presentation given during the September 25, 2009, teleconference that discussed the success of the Program was debated, and the Subcommittee members ultimately agreed on the meaning behind the statement and that the Program was making progress toward this goal. The CTRP has made tremendous progress, particularly compared to other groups, and has leveraged its resources

well to extend its expertise. The energy and intellect of the group is commensurate with the Program's budget.

With regard to Charge Question 2, the members thought that the CTRP needed to learn from successes outside of the Program and investigate think tanks to determine whether it has explored every possible aspect. The Program has done a good job exploring such avenues within the Agency and with outreach efforts to the community of practice.

For Charge Question 3, the Program is at the forefront in terms of pushing the traditional testing paradigm and introducing innovative approaches. The changes taking place could be useful in the future. This charge question lends itself to programmatic examples. Therefore, the Subcommittee's report should include several such examples, including the transformation of toxicity testing. The Program is testing the Tox21 paradigm and learning about the associated strengths and weaknesses. The Subcommittee members agreed that there is a good deal of value in learning the limitations.

Dr. Clark described the manner he was using to respond to Charge Question 4. He planned to use Figure 4 in the Subcommittee materials. This allowed him to understand the projects, management priorities, and the efforts that the Program was addressing. The Subcommittee members discussed the STAR grant mandate, which is to train researchers on the developed methods. It was agreed that the Program is making the right use of the STAR centers. The Subcommittee response to this question should be populated with specific examples. The recommendations from the NGO also should be placed under this charge question.

In terms of Charge Question 5, the CTRP has mission-critical goals that it is meeting and that Program has shown its value in proving that a computational approach is necessary for the Agency to fulfill its mission. The Program provides a center of excellence that will extend computational toxicology expertise throughout EPA. Furthermore, the Agency will not be able to accomplish its strategic plan without NCCT. The Program must, however, have a rigorous quality assurance system in place for the models and software that it produces, and this should be addressed under Charge Question 4. The Subcommittee members agreed that the Center should be made permanent.

The Subcommittee members finalized their plans to assemble the draft report. The goal is to have the report vetted at the December 2009 BOSC Executive Committee meeting so that the Program can receive it before February 2010 when the NCCT is scheduled to end. Dr. Daston thanked everyone for their participation and adjourned the meeting at 2:27 p.m.

## Action Items

- ✧ Subcommittee members will send their draft charge question responses via e-mail to Ms. Kowalski (copying Dr. Daston) by October 10, 2009.
- ✧ Subcommittee members should send comments on the charge questions to which they were not assigned via e-mail directly to the Subcommittee members assigned to respond to the questions prior to October 10, 2009.
- ✧ Ms. Kowalski will assemble the Subcommittee members' charge question responses into a draft report and forward it to the Subcommittee members.
- ✧ Subcommittee members will review the draft report and be prepared to discuss it on the October 21, 2009 conference call.

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**COMPUTATIONAL TOXICOLOGY SUBCOMMITTEE**
**AGENDA**
**September 29–30, 2009**
Hilton Raleigh-Durham Airport at Research Triangle Park
4810 Page Creek Lane
Durham, NC 27703

**Tuesday, September 29, 2009**

| | | |
|---|---|---|
| 12:00 noon – 12:30 p.m. | Registration | |
| 12:30 p.m. – 12:40 p.m. | Welcome and Introductions<br>- New Subcommittee Members<br>- Draft Charge<br>- Meeting Agenda | Dr. George Daston, Subcommittee Chair |
| 12:40 p.m. – 12:45 p.m. | DFO Remarks | Ms. Lori Kowalski, Office of Research and Development (ORD) |
| 12:45 p.m. – 1:00 p.m. | Computational Toxicology Research Program (CTRP)—Critical Component of EPA Science in the 21st Century | Mr. Lek Kadeli, ORD Acting Assistant Administrator (AA) |
| 1:00 p.m. – 1:45 p.m. | CTRP Overview<br><br>(NCCT) | Dr. Robert Kavlock, Director, National Center for Computational Toxicology |
| 1:45 p.m. – 2:15 p.m. | Introduction to Poster Session I: Informatics, Exposure Science, ORD, and External Partners | Dr. Ann Richard, NCCT |
| 2:15 p.m. – 4:15 p.m. | Poster Session I | Subcommittee/ORD |
| 4:15 p.m. – 5:15 p.m. | Poster Session I: Discussion | Subcommittee/ORD |
| 5:15 p.m. – 6:15 p.m. | Comments on the CTRP | Dr. Peter Preuss, Director, ORD/National Center for Environmental Assessment; Mr. Jim Jones, Deputy AA, EPA/Office of Prevention, Pesticides, and Toxic Substances; Dr. John Bucher, Associate Director, National Toxicology Program, National Institutes of Health; Dr. Cal Baier-Anderson, Senior Health Scientist, Environmental Defense Fund |
| 6:15 p.m. | Recess | |

**Wednesday, September 30, 2009**

| | | |
|---|---|---|
| 8:00 a.m. – 8:30 a.m. | Introduction to Poster Session II: High Throughput Screening, Toxicity Predictions, Virtual Tissues, and Uncertainty Analysis | Dr. Thomas Knudsen, NCCT |
| 8:30 a.m. – 10:30 a.m. | Poster Session II | Subcommittee/ORD |
| 10:30 a.m. – 11:30 a.m. | Poster Session II: Discussion | Subcommittee/ORD |
| 11:30 a.m. – 12:00 noon | CTRP Future: Providing High Throughput Decision Support Tools for Screening and Assessing Chemical Exposure, Hazard, and Risk | Dr. David Dix, Acting Deputy Director, NCCT |
| 12:00 noon – 12:15 p.m. | Public Comment | |
| 12:15 p.m. – 1:15 p.m. | Working Lunch | Subcommittee |
| 1:15 p.m. – 3:30 p.m. | Subcommittee Working Time | Subcommittee |
| 3:30 p.m. | Adjourn | |