COMPUTATIONAL TOXICOLOGY SUBCOMMITTEE

Conference Call Summary
Friday, September 25, 2009
12:00 – 1:00 p.m. Eastern Time

Welcome and Overview

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

Dr. George Daston, Chair of the Board of Scientific Counselors (BOSC) Computational Toxicology Subcommittee, welcomed the Subcommittee members to the teleconference and explained that the purpose of the conference call is to discuss next week's face-to-face meeting and ensure that all of the Subcommittee members understand the goals of the review. Each Subcommittee member has received a draft charge with five questions. The Subcommittee's job is to review the Computational Toxicology Research Program with the five charge questions in mind and produce a report that will consist of the Subcommittee responses to the charge questions. He noted that the Program orientation, materials, and information that will be presented at the face-to-face meeting are provided to the Subcommittee members to assist them in addressing the charge questions. This review is particularly important because it evaluates the progress of the Program during the previous 5 years, and the Subcommittee will have the major responsibility of making a recommendation on the continuation of the National Center for Computational Toxicology (NCCT). Dr. Daston asked the Subcommittee members to determine the charge questions on which they would like to work. Two to three people will be assigned to each of the first four questions, and all of the Subcommittee members will contribute to the response to the fifth question, on which Dr. Daston will take the lead. Following Dr. Daston's overview of the teleconference, each of the Subcommittee members present on the call introduced themselves.

Designated Federal Officer Remarks

Ms. Lorelei Kowalski, U.S. Environmental Protection Agency (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 and took roll. As the DFO, Ms. Kowalski ensures that all FACA requirements are met and that records of BOSC deliberations are made public. The minutes are being recorded by a contractor who will prepare a summary of the conference call and, following review by the Subcommittee members and certification by the Chair, will be available on the BOSC Web Site. All public meetings of the Subcommittee must be published in the *Federal Register* at least 15 days prior to the meeting and an electronic docket established. The electronic docket can be accessed at http://www.regulations.gov; the docket number is EPA-HQ-ORD-2009-0688. Regarding financial conflict of interest, Ms. Kowalski worked with officials to ensure that all ethics requirements were met satisfactorily. If a Subcommittee member discovers a conflict of interest during deliberations, the individual must notify the DFO immediately. This teleconference was convened to receive an overview of the Program, discuss any questions on the Program materials, and organize for the face-to-face meeting. The Subcommittee members should have received the PowerPoint presentation for the overview via e-mail on Thursday, September 24, 2009. Although there were no advance requests for comment from the public, an opportunity for public comment will be provided at 12:50 p.m.

Ms. Kowalski noted that the Subcommittee members should have received their travel itineraries for the face-to-face meeting. She asked members who had questions or had not received their itinerary to contact Troy Rutkofske at 202-564-5236.

Overview of the Computational Toxicology Research Program

Dr. Robert Kavlock, EPA/ORD/NCCT Director

Dr. Robert Kavlock, Director of the NCCT, explained that the Computational Toxicology Research Program began in Fiscal Year (FY) 2002 following Congress's request that EPA dedicate financial resources to new approaches to examining toxicity. The NCCT was established in 2005. This is the fourth review of the Program and/or NCCT in 54 months. The mission of the Program is to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals. The specific mission that has evolved during the last few years is to provide the Agency with decision-support tools for high-throughput screening, risk assessment, and risk management. The research plan is comprised of three components: NCCT, the Science To Achieve Results (STAR) grants program, and additional ORD input. The NCCT receives approximately 50 percent of funding and personnel resources of the Program. Approximately 25 percent of the Program's resources are dededicated to the STAR program. STAR funding in the area of computational toxicology is provided to academic centers rather than funding to individual researchers. Three centers have been established, one at the University of Medicine and Dentistry of New Jersey and two at the University of North Carolina at Chapel Hill. A fourth center presently is being established at the University of Houston. The remaining 25 percent of resources support collaborations with the National Health and Environmental Effects Research Laboratory (NHEERL) and National Exposure Research Laboratory (NERL). Additionally, the Program has some interaction with the National Center for Exposure Assessment. Dr. Kavlock explained that computational toxicology is funded via a line item (a 'program project') in EPA's budget.

Dr. Kavlock provided a brief overview of ORD's organization, including its national centers and laboratories. The NCCT reports directly to the Immediate Office of the Assistant Administrator for Research and Development and has approximately 20 staff members. *A Framework for a Computational Toxicology Research Program* was created in 2003 by a cross-organizational team within ORD. The framework was reviewed by the Science Advisory Board (SAB). The document focuses on types of problems facing environmental protection from the perspective of health and ecological effects and the tools becoming available in information technology and computational methods in molecular biology that could be applied to those problems. The framework document identified three long-term goals (LTGs): (1) improve linkages in the source-to-outcome paradigm, (2) provide predictive models for hazard identification, and (3) improve quantitative risk assessment.

The Program's first implementation plan focused on promoting EPA as an Agency that efficiently characterizes exposure, hazard, and risk through the widespread use of modern biological tools, information technologies, and computational models. Program challenges that were presented during the BOSC review in December 2007, included (1) hiring and integrating personnel under the Title 42 hiring authorization that allows external scientists to be hired for 5-year renewable terms, (2) implementing the ToxCast™ Program, (3) collaborating with other ORD laboratories and centers, (4) establishing effective extramural partnerships (e.g., STAR centers), (5) developing a Web presence, (6) surveying the use of quantitative methods in EPA risk assessments, and (7) bringing analytic tools to EPA operations.

The third BOSC review made a number of suggestions for the Program, including that it:

- ✧ Ensure that risk assessors are included in the research planning process and present during subsequent reviews.
- ✧ Make databases useful to clients.

- ✧ Articulate the use of ToxCast™ in risk assessment.
- ✧ Involve program offices in the virtual tissue projects.
- ✧ Provide a more detailed timeline for ToxCast™ beyond FY08.
- ✧ Delineate and prioritize key milestones for the virtual-Liver (v-Liver™) and virtual-Embryo (v-Embryo™) projects.
- ✧ Provide milestones for the arsenic biologically based dose response project.
- ✧ Develop structural specifications for heterogeneous ToxCast™ database.
- ✧ Be cautious on reliance on natural language processing for extraction of information into databases.
- ✧ Identify and enlist supporters for the v-Embryo™ project.
- ✧ Identify analytical use cases for ToxCast™ databases and release data early.

The second generation implementation plan has addressed the above BOSC remarks and suggestions and looks toward the future. The major differences between the two implementation plans include collapsing the three LTGs into one, expanding beyond hazard prioritization, supporting EPA's Strategic Plan for Evaluating the Toxicity of Chemicals, anticipating ORD's integrated multidisciplinary program on improving chemical risk management, and decreasing the emphasis on physiologically based pharmacokinetic (PBPK) models and chemical-specific efforts. The rationale for combining the three LTGs into one was that many of the projects were cross-cutting, and it became difficult to determine which projects belonged in which LTG. The de-emphasis on PBPK models was so that strong efforts in this area by NHEERL and the National Exposure Research Laboratory (NERL) were not duplicated.

Dr. Kavlock provided a brief overview of the Program's budget history. The FY 2010 budget includes 33 full-time equivalents, 22 of which are assigned to the NCCT, and a $19 million budget, of which approximately $12 million will be allotted to the Center.

Dr. Kavlock then reviewed the list of informational materials that the Subcommittee members were sent for the review, including the face-to-face meeting agenda; charge questions; Computational Toxicology Implementation Plan for FY09–FY12; poster abstracts; scientist biosketches, training, outreach, leadership, and bibliographic information; and previous BOSC reviews and ORD responses. Dr. Kavlock briefly introduced the five charge questions and provided an overview of the agenda for the face-to-face meeting.

Dr. James Clark asked whether the scope of the Program had been decreased when the three LTGs were collapsed into one. Dr. Kavlock responded that the Program did not change its scope or focus, which ultimately is to provide decisions support tools to the Agency. The simple, descriptive goal is more articulate, but there has been no change in content.

Dr. Daston asked for clarification regarding the content of the posters, and Dr. Kavlock responded that the posters include information that looks toward the future. In response to previous suggestions by the BOSC, the posters will be in a format similar to those presented at scientific meetings rather than broad overviews.

Dr. Daston noted that a great deal would be learned from the posters at the face-to-face meeting. To ensure that all of the posters receive the necessary amount of attention, he will designate specific

Subcommittee members to review certain posters at the face-to-face meeting. Dr. Lawrence Hunter reminded Dr. Daston and the other Subcommittee members that he would be attending the meeting by teleconference and would not be able to take the lead on any of the posters or the charge questions, but he would provide his input where he could.

Public Comment

Ms. Kowalski called for public comment at 12:50 p.m. No comments were offered.

Face-to-Face Meeting
Dr. George Daston, The Procter & Gamble Company, Subcommittee Chair

Dr. Daston asked the Subcommittee members to identify the charge questions that they would like to address. He received the following responses:

Subcommittee Member	Charge Question(s)
James Clark	2, 4
Richard T. Di Giulio	3
Ali Faqi	1, 5
Lawrence Hunter	2, 4
M. Moiz Mumtaz	1, 5
Dennis Paustenbach	2
Santiago Schnell	Any
Cynthia Stokes	1, 2, 4
Katrina Waters	3, 4

Dr. Daston said he will consider these requests and make the assignments prior to the face-to-face meeting. He asked the Subcommittee members to familiarize themselves with the charge questions and implementation plans before the meeting. Dr. Daston will e-mail the writing assignments to Ms. Kowalski, who will forward them to the Subcommittee members prior to the face-to-face meeting.

Dr. Dennis Paustenbach confirmed with Dr. Daston that the Subcommittee members would not meet on Monday, September 28, 2009, before the face-to-face meeting commences on Tuesday, September 29, 2009.

Dr. Daston thanked everyone for their participation and adjourned the teleconference at 12:54 p.m.

Action Items

- ✧ The Subcommittee members will familiarize themselves with the charge questions and the Program implementation plans before the face-to-face meeting.

- ✧ Dr. Daston will assign the charge questions to the Subcommittee members and e-mail the assignments before the face-to-face meeting to Ms. Kowalski, who will forward them to the Subcommittee members.

PARTICIPANTS LIST

Subcommittee Members

George P. Daston, Ph.D., Chair
Research Fellow
The Proctor & Gamble Company
Miami Valley Laboratories

James R. Clark, Ph.D., Vice-Chair
Distinguished Scientific Associate
ExxonMobil Research and Engineering Company

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Agency for Toxic Substances and Disease Registry

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ChemRisk, Inc.

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University of Michigan Medical School

Katrina Waters, Ph.D.
Computational Biology & Bioinformatics Group
Battelle

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Office of Research and Development

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Other Participants

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Office of Management and Budget

Michael Hagan
Office of Management and Budget

Maria Hegstad
Risk Policy Report

Contractor Support

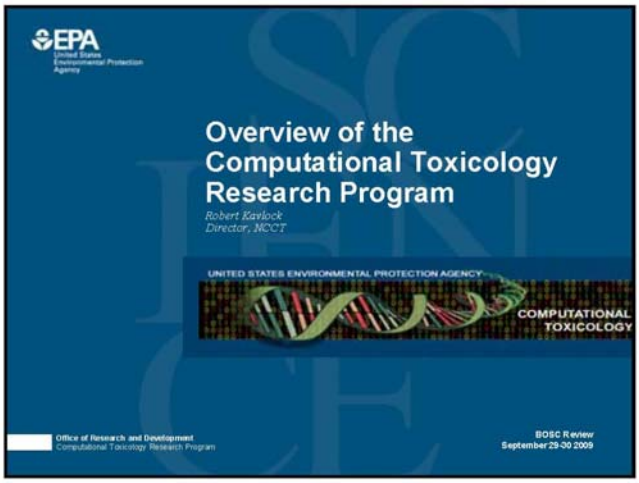
Kristen LeBaron, M.S.
The Scientific Consulting Group, Inc.

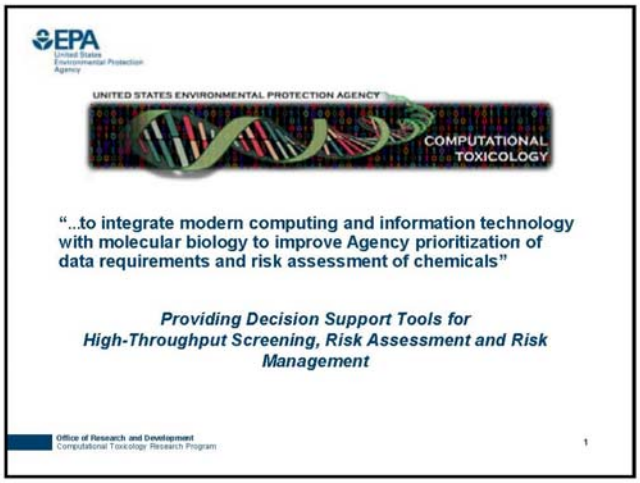
COMPUTATIONAL TOXICOLOGY SUBCOMMITTEE
AGENDA
Friday, September 25, 2009
12:00 noon – 1:00 p.m. Eastern Time

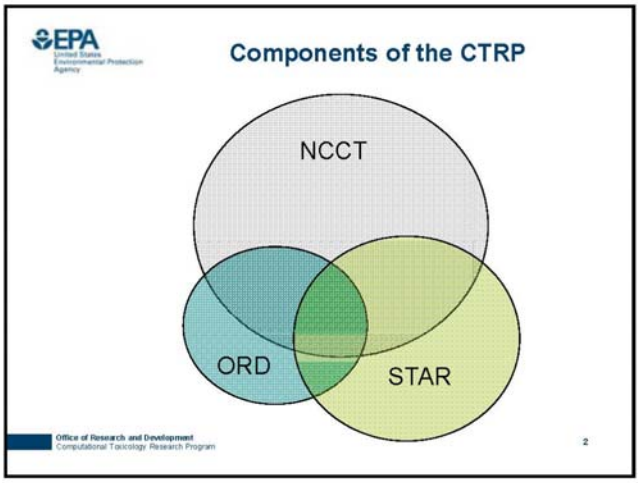
CONFERENCE CALL
Participation by Teleconference Only

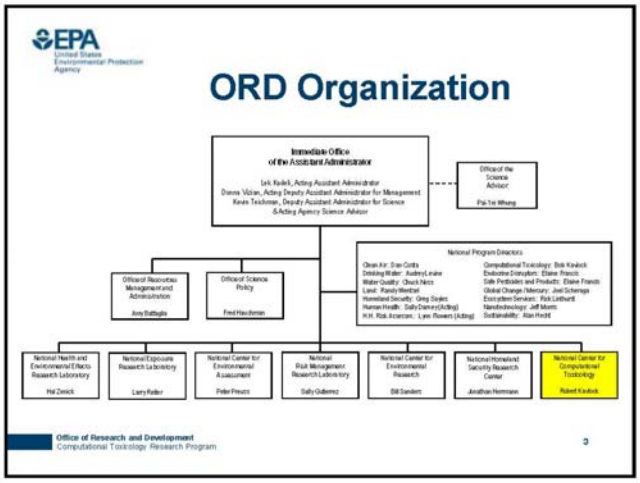
12:00 noon	Welcome and Overview - Purpose of Teleconference - New Member Introductions - Draft Charge	Dr. George Daston, Chair Computational Toxicology Subcommittee
12:15–12:20 p.m.	DFO Remarks	Lori Kowalski, Office of Research and Development
12:20–12:50 p.m.	Overview of the Computational Toxicology Research Program - Materials for the Review	Dr. Robert Kavlock, Director National Center for Computational Toxicology (NCCT)
12:50–12:55 p.m.	Public Comment	
12:55–1:00 p.m.	Face-to-Face Meeting - Outstanding Issues	Dr. George Daston, Chair, Computational Toxicology Subcommittee
1:00 p.m.	Adjourn	

Computation Toxicology Research Program Overview Slide Presentation









Computation Toxicology Research Program Overview Slide Presentation (Cont'd)

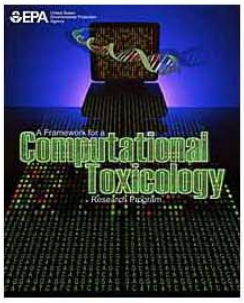
The Framework for a CompTox Program (2003)

Goals:

- Improve Linkages in the Source to Outcome Paradigm
- Provide Predictive Models for Hazard Identification
- Improve Quantitative Risk Assessment (Dose, Species, Chemical)

Success:

- Measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern



1st Generation Implementation Plan (circa 2006)

An Agency that efficiently characterizes exposure, hazard and risk through the wide spread use of modern biological tools, information technologies, and computational models

2003 2006 2008

sBOSC III - Current Challenges (Dec 2007)

- Hiring, and integrating, the T42s
- Implementing ToxCast
- Collaborations with other ORD L/Cs
- Establishing effective extramural partnerships, including the STAR Centers
  - –Issuance of new RFA in FY07
- Web presence
- Surveying the use of quantitative methods in EPA risk assessments
- Bringing analytic tools to EPA operations
  - –Chemoinformatic, Bioinformatic, and Visual Analytic

Suggestions of sBOSC III

- Ensure that risk assessors are included in the research planning process and present at the next review
- Make databases useful to clients
- Articulate use of ToxCast in risk assessment
- Involve program offices in the virtual tissue projects
- Provide more detailed timeline for ToxCast beyond FY08
- Delineate and prioritize key milestones for the v-Liver and v-Embryo projects
- Provide milestones for the arsenic BBDR project
- Develop structural specifications for heterogeneous ToxCast database
- Caution in reliance on NLP for extraction of information into databases
- Identify and enlist supporters for the v-Embryo project
- Identify analytical use cases for ToxCast databases and release data early

Computation Toxicology Research Program Overview Slide Presentation (Cont'd)

2nd Generation Implementation Plan

U.S. EPA OFFICE OF RESEARCH AND DEVELOPMENT
COMPUTATIONAL TOXICOLOGY RESEARCH PROGRAM
IMPLEMENTATION PLAN FOR FISCAL YEARS 2009-2012

Providing High Throughput Decision Support Tools for Screening and Assessing Chemical Exposure, Hazard and Risk

BOSC Review Draft- 24 August, 2009

DISCLAIMER:

Major Changes to Implementation Plan

- Contraction from three LTGs to one
  - Providing High Throughput Decision Support Tools for Screening and Assessing Chemical Exposure, Hazard and Risk
- Expansion beyond hazard prioritization
  - Increased emphasis on Exposure Prioritization (NERL)
  - Input into NexGen risk assessments (NCEA)
  - Systems approaches to tissue damage (NHEERL, STAR)
- Support for EPAs Strategic Plan for Evaluating the Toxicity of Chemicals
  - Tox21 Consortium (NTP, NCGC (plus FDA and JRC))
- Anticipation of ORDs integrated multidisciplinary program on improving chemical risk management (FY11)
- Decrease Emphasis:
  - PBPK Models, Chemical-specific efforts

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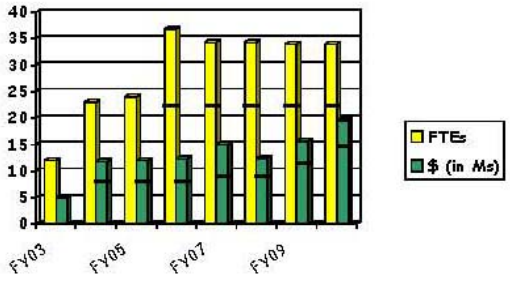
CTRP Budget History



Computation Toxicology Research Program Overview Slide Presentation (Cont'd)