Lessons Learned, Challenges, and Opportunities: The US Endocrine Disruptor Screening Program

April 23-24, 2013
North Carolina Biotechnology Center
Research Triangle Park, North Carolina

WORKSHOP ORGANIZED BY

TERA
Toxicology Excellence for Risk Assessment

Welcome!

April 23, 2103

Dear Colleagues:

Welcome to this workshop on **Lessons Learned, Challenges, and Opportunities: The US Endocrine Disruptor Screening Program.** We are pleased you have chosen to attend this workshop and join with colleagues from a broad range of affiliations to explore and discuss the current state of knowledge and experience with the Endocrine Disruptor Screening Program (EDSP) assays. The workshop has been designed to focus on the science and experience to date and to identify lessons learned that can be used to inform ongoing and future efforts to determine the endocrine disruption potential of chemicals.

We invite you to participate fully in this workshop. Through this workshop we are attempting to capture the experience and opinions of individuals that have a professional interest in the EDSP, whether performing the assays, interpreting the data from them, or being required to provide the data to meet regulatory requirements for evaluation of potential hazards and risks. We have invited knowledgeable and engaging speakers to provide their perspectives on what we believe are the most important facets of the EDSP; talks will address the current battery of Tier 1 assays, how information from Tier 1 can be used to perform weight of evidence and mode of action assessments, and to provide perspectives on the future of endocrine screening and testing. The poster session and reception Tuesday evening is an opportunity for on-site attendees to mix and mingle, view posters, and discuss the latest science with colleagues.

At the end of each session you will have the opportunity to ask questions of the speakers and panel discussants. To be inclusive and provide as broad and balanced discussion as possible, the final session is intended to capture the additional experience and expertise of the interested scientists participating in this workshop. We encourage you to share your opinions and perspectives on the important issues related to screening chemicals for endocrine disruption potential. In addition to the 150 attendees at the North Carolina Biotechnology Center, we are pleased that an additional hundred persons are attending remotely through a webinar. By broadcasting the workshop via webinar we are attempting to make the workshop as accessible as possible and reach all those who are interested. Information on how webinar attendees can submit comments or questions is found in the Webinar section of this program.

The major overarching themes that emerge from this session will be summarized in a workshop report and publication, so that all those interested may learn from the experience and insights shared and discussed. A brief report will be made available at http://www.tera.org/peer/edsp/ shortly after the workshop. A publication is also planned for ALTEX.

We thank our many sponsors who have provided funds to make this workshop possible, and the many people including our speakers and panel discussants who have contributed their valuable time to make this workshop a success. This workshop was organized by a committee of volunteers from government, industry, academia, and animal welfare organizations. The committee was assisted by staff from Toxicology Excellence for Risk Assessment (TERA). We hope you find the workshop a productive and enjoyable experience.

Sincerely,

The Workshop Organizing Committee

This page intentionally blank

Table of Contents

This page intentionally blank

Workshop Information

The Endocrine Disruptor Screening Program (EDSP) was implemented by the US Environmental Protection Agency (EPA) by issuing the first round of test orders in 2009 for information on 67 chemicals (59 pesticide active ingredients and eight pesticide inert ingredients). The request includes information from a battery of screening assays, referred to as Tier 1, includes five *in vitro* assays, four mammalian assays, and two non-mammalian assays. Tier 1 screening of this initial list of chemicals has now been completed and the data have been submitted to EPA. This screening has yielded large volumes of data derived from numerous laboratories and on a variety of chemical classes.

The results from this first phase of testing represent the first comprehensive experience with these assays individually and as a battery in a regulatory context. The experience and insight of the practitioners and laboratories conducting the screening provides an unprecedented resource for informing the future success of the program.

This workshop brings together multiple stakeholders for the opportunity to review and discuss the challenges and lessons learned from the initial experiences with Tier 1 screening assays in an open forum. Such an open meeting with all stakeholders – including Federal Regulatory Agencies, NGOs, industry, contract laboratory scientists, and academic researchers - is critical - and timely - to best use this collective experience for potential improvements in Tier 1 assays, and to further advance our ability to assess endocrine disruption. All stakeholders and interested parties have been invited to participate.

Workshop Objectives

This open workshop has been designed to focus on the science and experience to date and is not intended to be a forum to discuss individual chemicals and their performance in the Tier 1 screening assays. Lessons learned and the ensuing discussion/outcomes at this workshop will support the use and implementation of the proposed advancements described in the EDSP21 (Endocrine Disruptor Screening Program – 21st Century) and TT21C (Toxicity Testing in the 21st Century) visions.

The overarching workshop objectives are to:

- Provide participants with knowledge gained and lessons learned, including assay performance, by laboratories and organizations that performed testing on the initial list of chemicals.
- Identify challenges and best practices in the technical and biological assessment of endocrine modulation.

- Discuss insights on the challenges of integrating and interpreting the data collected from Tier 1 assays (e.g., weight of evidence approaches and signature patterns).
- Explore insights on biological mechanisms relevant to endocrine modulation and their application in assay result interpretation and decision making.
- Engage perspectives from a range of stakeholders, including academia, government, industry, and NGOs on the future implementation, challenges, and opportunities regarding how to best address the challenges and opportunities for screening potential endocrine modulating chemicals in the 21st century.

Organizing Committee

The idea for this workshop originated several years ago and an organizing committee of individuals from various stakeholders and interested organizations have been actively working for the last six months to actively bring this workshop to fruition. Organizing Committee members include:

- Rick Becker, American Chemistry Council
- Susan Borghoff, Integrated Laboratory Systems, Co-Chair
- Warren Casey, National Institute of Environmental Health Sciences
- Thomas Hartung, Center for Alternatives to Animal Testing, Johns Hopkins University
- Michael Holsapple, Battelle
- Daland Juberg, Dow AgroSciences, Co-Chair
- Sue Marty, The Dow Chemical Company
- Ellen Mihaich, Endocrine Policy Forum
- Glen Van Der Kraak, University of Guelph
- Mike Wade, Health Canada
- Kate Willett, Humane Society of the United States

Sponsors

We are grateful to the many organizations that made this workshop possible through their monetary and in-kind contributions. Without this support, this workshop would not be possible. A special thanks to the North Carolina Biotechnology Center.

- ABC Laboratories, Inc.
- Alkylphenols & Ethoxylates Research Council
- Alliance for Risk Assessment
- American Chemistry Council
- American Cleaning Institute
- American Petroleum Institute
- AMVAC Chemical Corporation
- BASF Corporation
- Battelle
- Bayer CropScience
- Center for Alternatives to Animal Testing (CAAT/Johns Hopkins)
- CeeTox, Inc.
- Cheminova
- Council of Producers & Distributors of Agrotechnology
- Consumer Specialty Products Association
- CropLife America
- Doerenkamp-Zbinden Foundation
- Dow AgroSciences
- DuPont
- Endocrine Policy Forum
- ExxonMobil Biomedical Sciences, Inc.
- Grocery Manufacturers Association
- Gowan
- Huntingdon Life Sciences/LSR Associates
- Human Toxicology Project Consortium
- The Humane Society of the United States
- Integrated Laboratory Systems, Inc.
- Makhteshim Agan of North America, Inc.
- Monsanto
- MTBE Consortium
- North Carolina Biotechnology Center
- Personal Care Products Council
- Smithers Viscient
- Society of Chemical Manufacturers and Affiliates, Inc.
- Styrene Information and Research Council
- Society of Toxicology
- SOT Regulatory Safety Evaluation Specialty Section (RSESS)
- SOT Ethical, Legal and Social Issue Specialty Group (ELSI)
- Syngenta
- Toxicology Excellence for Risk Assessment (TERA)
- WIL Research
- Wildlife International

Poster Session

We are pleased to have a poster session and mixer as part of our program, to provide the on-site attendees the opportunity to further discuss issues and learn of current research and activities. The poster session will be on Tuesday evening from 5 PM to 7 PM. Nearly 30 posters will be on display, with authors present to discuss their work. A separate listing of posters and poster abstracts is available at the registration table. Complimentary appetizers and beverages will be available, courtesy of our workshop sponsors.

Toxicology Excellence for Risk Assessment (TERA)

TERA is pleased to serve as the facilitator and host for this workshop. TERA is an independent non-profit organization dedicated to the best use of toxicity data for risk assessment (see www.tera.org). TERA is experienced in the coordination and facilitation of multi-stakeholder workshops and peer review, and has worked closely with the organizing committee since last fall to plan and develop this workshop.

Alliance for Risk Assessment (ARA)

The workshop is a project under the Alliance for Risk Assessment (*ARA*). *ARA* is a collaboration of organizations that fosters the development of technical chemical risk assessment products and services, through a team effort of specialists and organizations dedicated to protecting public health by improving the process and efficiency of risk assessment, and to increasing the capacity for developing risk values to meet growing demand. All *ARA* projects are vetted by a Steering Committee comprised of federal and state government, academic, and environmental NGO perspectives, to promote scientific relevance and avoid duplication of effort. As an *ARA* project, this project was led by an independent, nonprofit organization, performed in an open and transparent manner, and the results will be made publically available through numerous means, including at www.allianceforrisk.org.

Workshop Agenda

This page intentionally blank

Lessons Learned, Challenges, and Opportunities: The US Endocrine Disruptor Screening Program

TUESDAY, APRIL 23, 2013

7:15 - 8:15 **Registration and poster set up**

Welcome and Introductions

8:15 - 8:45 **Welcome and Workshop Overview - *Dr. Daland Juberg, Workshop Chair***
"Why are we here?" - *EDSP Workshop Organizing Committee*

Session I - Performance of the EDSP Tier I Screening Assays; Insights from Conducting Assays for List 1 Chemicals

This session will focus on the conduct and performance of all 11 Tier 1 assays; areas of discussion will include the ease of conduct, consistency in performance along with specific challenges and solutions. Topics will include dose selection for identification of the MTD and the most effective and efficient range finding studies. This session will also include lessons learned from companies/CROs involved in conducting these assays to focus on improvement and increased efficiency in future testing. Focus will be on the interpretation of the individual assays with an emphasis on the challenges of interpreting apical assays. Each presentation will include a discussion on performance criteria for each of the respective assays. Discussion will take place after each presentation with a focus on capturing the audiences' input and experiences with the Tier 1 assays.

8:45 - 8:50 **Introduction to Session I - *Dr. Susan Borghoff, Session Chair***

8:50 - 9:30 **Review of *in vitro* Assays - Validation Results and Methods for Improving *In Vitro* Tier 1 Endocrine Disruption Screening Assays - – *Dr. Colleen Toole, Ceetox***

9:30 - 10:10 **Review of in vivo Mammalian Assays - Challenges and Considerations for Conducting and Interpreting These Screening Assays - *Dr. Leah Zorrilla, ILS, Inc.***

10:10- 10:45 **BREAK**

10:45 - 11:30 **Review of Non-mammalian Assays - Challenges and Potential Solutions for the Conduct and Interpretation of the Amphibian Metamorphosis Assay and the Fish Short Term Reproduction Assay - – *Dr. Katherine Coady, The Dow Chemical Company***

11:30 - 12:15 **Panel Discussion and Audience Q&A :** ***Dr. Ronald Biever, Smithers Viscient; Dr. Donald Stump, WIL Research; Dr. Kun (Sue) Yi, Syngenta Crop Protection***

12:15 - 1:15 **LUNCH**

Session II - Practical Applications of Tier 1 Data

The focus of this session will be how information from the current Tier 1 battery can be applied to identifying potential endocrine modes of action (MOA) and performing a weight of evidence (WOE) assessment to evaluate potential interactions with the estrogen, androgen or thyroid pathways. First, Tier 1 assay redundancy will be examined along with the use of Tier 1 data to identify potential endocrine MOAs. General principles of WOE and the EPA's WOE document for evaluating Tier 1 endocrine results will be discussed. An information framework will be introduced that can be used for WOE assessments and/or differentiating potential MOAs. Lastly, a case study will be presented to show one approach aimed at improving the objectivity and transparency of endocrine WOE assessments.

1:15 - 1:20 **Introduction to Session II -** ***Dr. Sue Marty, Session Chair***

1:20 - 2:00 **A Two-Tiered-Testing Decision Tree for Assays in the USEPA-EDSP Screening Battery: Using 15 years of experience to improve screening and testing for endocrine active chemicals -** ***Dr. L. Earl Gray Jr., US Environmental Protection Agency***

2:00 - 2:40 **Pulling it Together – Preparing for a Weight of Evidence Assessment on Endocrine Activity –** ***Dr. Sue Marty, The Dow Chemical Co.***

2:40 - 3:15 **BREAK**

3:15 - 3:55 **A Weight of Evidence Approach to Examine Endocrine Activity -** ***Dr. Christopher Borgert, Applied Pharmacology & Toxicology, Inc.***

3:55 - 4:45 **Panel Discussion and Audience Q&A:** ***Patricia Bishop, PETA; Dr. Kevin Crofton, US EPA; Dr. Ellen Mihaich, ER^2 and Endocrine Policy Forum***

4:45 - 5:00 **Day One Wrap Up and Prelude to Day Two -** ***Dr. Daland Juberg, Workshop Chair***

Poster Session and Mixer

Nearly 30 posters will be on display, with authors present to discuss their work. A separate listing of posters and poster abstracts is available at the registration table. Complimentary appetizers and beverages will be available, courtesy of our workshop sponsors.

5:00 - 7:00 **Poster Session and Mixer -** ***Dr. Susan Borghoff, Session Chair***

WEDNESDAY, APRIL 24, 2013

7:30 - 8:00 **Registration**

Welcome Back and Poster Review

8:00 - 8:25 **Welcome Back**
Report from Poster Session, *Dr. Richard Becker, American Chemistry Council*

Session III- Considerations in the Future of Endocrine Testing

In 2012, the EPA announced plans for an Endocrine Disrupter Screening Program for the 21st Century (EDSP21), a multi-year transition from the current EDSP Tier I screens and Tier 2 tests to a more efficient use of computational toxicology and high throughput *in vitro* assays. The initial goal is to allow the agency to more quickly and cost-effectively prioritize substances for entering into the EDSP, and the ultimate goal is to eventually replace some, or all of the existing EDSP assays. The promises, opportunities, challenges, and concerns associated with the tools and approaches to implement the 2007 NRC report, "Toxicity Testing in the 21st Century: A Vision and Strategy", have been widely discussed and debated in recent years. The goal of this session will be to provide some perspective on how the future of endocrine screening and testing is being shaped by the integration of Tox21 tools.

8:25 - 8:30 **Introduction to Session III - *Dr. Warren Casey, NIEHS; Dr. Jack Fowle, EPA, retired; and, Dr. Richard Becker, American Chemistry Council; Session Co-Chairs***

8:30 - 9:00 **EPA ToxCast HTS Assays and Prediction Models for Estrogen, Androgen, Thyroid and Steroidogenesis Pathways - *Dr. David Dix, EPA NCCT***

9:00 - 9:30 **Tier 1 and Done: Developing *in vitro* Cell-based Assays of Endocrine Pathways Sufficient by Themselves for 21st Century Risk Assessment – *Dr. Mel Andersen, The Hamner Institutes for Health Sciences***

9:30 - 10:00 **Mapping the Human Toxome by Systems Toxicology - Using ED as a Proof of Concept - *Dr. Thomas Hartung, Center for Alternatives to Animal Testing, Johns Hopkins***

10:00- 10:15 **BREAK**

10:15 - 10:35 **The Future of Endocrine Screening: An Animal Welfare Perspective – *Dr. Catherine Willett, Humane Society of the United States***

10:35 - 10:55 **Road Map for Building Scientific Confidence in HTP Assays-** ***Dr. David Geter, Bayer CropScience***

10:55 - 11:15 **Designing the Next Generation of Sustainable Chemicals -** ***Thaddeus Schug, NIEHS***

11:15 - 12:00 **Panel Discussion and Audience Q&A**

12:00 - 12:45 **LUNCH**

Session IV - Participant Discussion

Through this workshop we are attempting to capture the experience and opinions of all individuals that have a professional interest in the EDSP, whether performing the assays, interpreting the data from them, or being required to provide the data to meet regulatory requirements for evaluation of potential hazards and risks. We have invited knowledgeable and engaging speakers to provide their perspectives on what we believe are the most important facets of the EDSP. However, to be inclusive and provide as broad and balanced assessment of the program as possible, we want to capture the additional experience and expertise of the interested scientists participating in this workshop. This last session is intended to provide workshop attendees with an opportunity to add additional thoughts, perspectives, concerns, the fruits of personal experience, and/or questions about the future of the program and how it addresses and likely impacts US and global challenges and opportunities. The major overarching themes that emerge from this session will be summarized in the final workshop summary report, with no identification or attribution to individuals. If workshop attendees have not heard their perspective articulated during the presentations or discussion over the course of the formal program, we encourage you to share them during the open microphone of Session IV. [Note: Due to the large number of participants and limited time, we will not be able to accommodate real-time input from webinar participants during this Session. We encourage those on the webinar to submit brief written comments after the workshop via the workshop webpage to provide additional comments or perspectives that were not covered; the webinar comments will be incorporated into the workshop summary report.]

12:45 - 2:30 ***Dr. James C. Lamb, IV, Exponent, Inc., Opening Remarks***

Dr. Michael Dourson, TERA, Facilitator

Closing Remarks

2:30 - 2:45 ***Dr. Daland Juberg, Workshop Chair***

Logistics

This page intentionally blank

Logistics

On-Site Logistics

The workshop is being held at:

North Carolina Biotechnology Center
15 TW Alexander Drive
Research Triangle Park, NC 27709-3547

If you are staying at the recommended hotels, a free shuttle is available to and from the workshop. Please be advised that the shuttles have limited capacity, and may be overcrowded. Please plan accordingly.

Driving directions between the hotels and the NC Biotechnology Center can be found at the back of the program. There is free onsite parking at the Center.

Meals

Lunch will be provided to workshop participants during Tuesday and Wednesday sessions. Coffee and light refreshments will be provided during the morning and afternoon breaks.
The Poster Session Tuesday evening will include a variety of appetizers and alcoholic and non-alcoholic beverages.

Webinar Logistics

We are pleased to be broadcasting this workshop to those offsite using WebEx. We hope in this way to make the talks and discussions available to a broader audience who was not able to attend in person. Due to facility limitations our webinar connections are limited to 100; **therefore we ask those who have registered for the webinar to not share their connection information with others as this may result in those who have registered not being able to log on**. Feel free to ask colleagues to join you and view the webinar via your computer

Webinar participants are invited to submit questions and comments for the Q&A periods by sending them to Oliver Kroner at kroner@tera.org. We will do our best to have these questions addressed during the Q&A session. However, due to the large number of participants, we anticipate receiving more questions than we will have time for, and apologize in advance if your question is not read during the workshop.

A special note regarding Session IV - Due to the large number of participants and limited time, we will not be able to accommodate real-time input from webinar participants during this the final session. We encourage those on the webinar to listen closely to what others are saying and to submit brief written comments after the workshop to provide additional comments or perspectives

that were not raised by those attending in person. These can be sent to kroner@tera.org. The webinar comments will be incorporated into the overall summary of Session IV that will be included in the workshop report. Because the workshop report will be brief, individual comments and names will not be identified, rather overarching themes and ideas will be summarized.

Workshop Evaluation

We want your feedback on this workshop. An evaluation form is available at http://www.tera.org/peer/edsp/.

Questions or Concerns? Please contact the TERA representatives - Oliver Kroner (c. 513-284-0899) or Jacqueline Patterson on site.

Biographies and Abstracts

This page intentionally blank

Workshop Co-Chairs

Daland Juberg, Dow AgroSciences

Dr. Daland R. Juberg is a toxicologist and North American leader of the Human Health Assessment Group within Dow AgroSciences (Indianapolis, IN). He received his PhD in Toxicology and a M.S. in Environmental Health Sciences, both from the University of Michigan. Professional experience spanning more than 20 years includes consultation with the International Center for Toxicology and Medicine and corporate applied and regulatory toxicology work for Eastman Kodak. He has worked at regional, national and international levels on matters involving health risk and regulatory decision-making. He is involved with several ILSI Task Forces including chair of the Biotech Harmonization TF and has maintained an avid interest in scientific outreach. He has served the Society of Toxicology as Chair of the Regulatory Affairs and Legislative Assistance Committee, Communications Committee (chair), and Congressional Task Force (chair), and is presently chairing the TSCA Task Force. He is Vice-President elect of the Regulatory and Safety Evaluation Specialty Section within SOT and is engaged in several Congressional efforts aimed at highlighting the importance of incorporating scientific information in legislation and regulation surrounding public health.

Dr. Susan Borghoff, ILS, Inc.

Susan Borghoff earned a B.S. in Chemistry from East Stroudsburg University and a MSPH and Ph.D. in Environmental Sciences and Engineering from The University of North Carolina (1987). She did her postdoctoral training at the Chemical Industry Institute of Toxicology (CIIT) and has been a Diplomate of the American Board of Toxicology since 1994. Dr. Borghoff was on the scientific staff at CIIT (1989-2006) where her research focused on understanding the mode-of-action by which chemicals cause cancer in rats through cytotoxic and an alteration in endocrine pathways, with a view to understanding the relevance of these responses for human risk assessment. She also focused on studying the developmental pharmacokinetics of endocrine active compounds. Dr. Borghoff has been the Director of the Investigative Toxicology Division at Integrated Laboratory Systems (ILS), since 2006. In 2009, Dr. Borghoff implemented a program to conduct the EDSP Tier I mammalian screening assays at ILS and since that time they have completed the testing of over 21 chemicals. Dr. Borghoff received the Frank R. Blood Award in 1994 for the best paper and a Society of Toxicology Risk Assessment Specialty Section Award in 2000. She is a member of a number of professional societies including ACT, NCSOT, and most active in the SOT (Council member 2009-2011, Program Committee, Education Committee and Awards Committee). She has been an Associate Editor for Toxicological Sciences and on the editorial board for Chemical Biological Interactions and Toxicology Letters. Dr. Borghoff has served as reviewer on a number of review/working groups for both National and International organizations; USEPA, NCI, IPCS, ECETOC, and IARC. She has also been a reviewer for the NIEHS: Superfund Basic Research Program Grant, Special Emphasis Panel for ADME Chemical Disposition in Mammals Contract, Engineered Nanomaterials: Linking Physical and Chemical Properties to Biology and USEPA Research Grants on Children's Health Issues.

This page intentionally blank

Session I - Performance of the EDSP Tier I Screening Assays; Insights from Conducting Assays for List 1 Chemicals

SESSION CHAIR

Dr. Susan Borghoff, ILS, Inc.

Please see Workshop Co-Chair biography above.

Review of *in vitro* Assays - Validation Results and Methods for Improving *in vitro* Tier 1 Endocrine Disruption Screening Assays

Dr. Colleen Toole, CeeTox

Colleen Toole, Ph.D. joined CeeTox in the position of Director of Project Management in 2008. She has grown the endocrine work at CeeTox into an internationally recognized platform. Dr. Toole graduated with high honors from the doctoral program at Tulsa University under the direction of Dr. Lamont Anderson in Molecular Biology. She pursued postdoctoral training at Martek Biosciences located in Columbia MD, working to develop and market proprietary technology "Rd Flip" (Recombinantly-derived Fluorescently-labeled Interrogation Probes) for high-throughput assays based upon cyanobacterial and red algal-derived fluorescent proteins (phycobilisomes and phycobiliproteins).

Dr. Toole developed assays and investigated kinase, phosphatase, methylase inhibitors and activators, utilizing a microfluidic platform while at Amphora Discovery in RTP, North Carolina. She was Team Leader for the AKT project. As Director of Molecular Biology at Cayman Chemical Company, she initiated and directed the molecular biology/protein expression core group. She was later named Manager of Preclinical Drug Discovery for Cayman Chemical. Dr. Toole has extensive experience in assay development utilizing various readouts including luminescence, absorbance, fluorescence, fluorescence polarization, FRET, TR-FRET and microfluidics. As Director of Project Management for CeeTox, she leads the scientific services division, managing the progress of all client studies, focused on endocrine activity as well as providing technical liaison to the sales team. Dr. Toole has received numerous research awards and has co-authored peer-reviewed articles and presented many papers at national scientific meetings.

Abstract

The Endocrine Disruption Screening Program (EDSP) was initiated by the Environmental Protection Agency (EPA) in order to develop a screening program to evaluate whether or not certain chemicals could have hormonal effects in humans. As a result Tier 1 assays, *in vitro* and *in vivo* were selected to evaluate estrogen, androgen and thyroid effects of commercial chemicals and

environmental contaminants. CeeTox has established and run reference compounds for these five *in vitro* Tier 1 assays (Steroidogenesis, Aromatase, ER and AR binding and ER transactivation) according to EPA protocols. Proficiency data was generated from reference compounds run in these Tier 1 *in vitro* assays using modifications that improved the assays by reducing false negative and false positive results. An example of these modifications is in the ER transactivation assay utilizing the hERα-Hela-9903 cell line where inclusion of solubility and cytotoxicity assessments can assist in data interpretation. Additional controls, such as including the strong antagonist, ICI 182,780 on each plate, allows for identification of non-specific (i.e., non-hERα-mediated) induction of the luciferase gene and assists in identifying false positives. Other modifications for the conduct of the Aromatase, ER and AR binding assays and Steroidogenesis assay will be discussed.

Review of *in vivo* Mammalian Assays - Challenges and Considerations for Conducting and Interpreting These Screening Assays

Dr. Leah Zorrilla, ILS, Inc.

Dr. Leah Zorrilla is the Program Manager of Reproductive and Endocrine Toxicology in the Investigative Toxicology Division of Integrated Laboratory Systems (ILS) where she joined in 2010. Prior to ILS, Dr. Zorrilla completed a postdoctoral co-op at the U.S. EPA/North Carolina State University where she conducted several reproductive toxicology studies using the EDSP Tier 1 in vivo assay guidelines. These studies screened the effects of pesticides and antibacterials on the rodent endocrine system. Dr. Zorrilla has authored or co-authored a number of papers and a book chapter on the Tier 1 in vivo EDSP assays. Dr. Zorrilla received her Ph.D. in Comparative Biomedical Sciences, Reproductive Endocrinology from North Carolina State University and her B.S. in Animal Science from the University of New Hampshire.

Dr. Zorrilla designs, coordinates, and directs hypothesis as well as regulatory-driven studies focused in areas of both reproductive and endocrine toxicology as well as general toxicology studies for both commercial and federal clients. She has extensive knowledge of the reproductive and endocrine toxicology standardized test guidelines including the EDSP Tier 1 in vivo assays. She has recently functioned as the Study Director on over 25 Tier 1 in vivo assays for EPA submission along with many dose range finding studies to determine maximum tolerated dose levels to use in these assays. She is knowledgeable of pertinent rules and regulations, policies, and standards for compliance to PHS, Animal Welfare Act, FDA, and USDA policies, EPA, OECD, and GLP standards, and ensures responsible, humane care of research animals. Dr. Zorrilla is an ad hoc reviewer for several reproductive toxicology journals and is an active member of the Society of Toxicology, the Society for the Study of Reproduction, and The Triangle Consortium of Reproductive Biology.

Abstract

The U.S. EPA Endocrine Disruptor Screening Program (EDSP) includes four mammalian assays to screen test substances for potential disruption of the estrogen, androgen, or thyroid hormone pathways. The EPA guidelines provide detail on the study design and conduct, in addition to performance criteria that need to be met in the conduct of these assays. The Uterotrophic Assay screens for potential estrogenic activity and can be performed in immature intact females or ovariectomized adult rats. Animals are administered the test substance for three days, and at termination the wet and blotted uterine weights are obtained. A positive estrogenic response in the assay is a significant increase in the uterine weights. The Hershberger Bioassay screens for both potential androgenic and anti-androgenic activity in the adult male castrated rat. Animals are administered test substance for ten consecutive days and at termination five androgen-dependent tissues are excised and weighed. A positive response in the agonist assay or antagonist assay is a significant increase or decrease, respectively, in at least two tissue weights compared to controls. The Male and Female Pubertal Development and Thyroid Function Assays screen for disruption of androgen (male), estrogen (female), and thyroid (both) hormone pathways. These assays are conducted during the peri-juvenile stages of development from approximately postnatal (PND) 22 to 42/43 (female) and 23 to 53/54 (male). The pubertal assays are designed to evaluate potential changes on the intact developing endocrine system through the measurement of various endpoints including the day of vaginal opening and estrous cyclicity (female), day of preputial separation (male), changes in tissue weights and serum hormone concentrations, and histopathological evaluation of selected tissues. Based on our experience and the experience of others with these four assays, each assay will be discussed with an emphasis on study conduct, dose selection, performance criteria, challenges, and solutions for the successful implementation of each assay. The results from these assays in addition to those obtained from complementary *in vitro* and non-mammalian *in vivo* assays, along with other scientifically-relevant information, will be reviewed by the U.S. EPA to determine the potential endocrine disruption of the test substance and if Tier 2 testing will be necessary.

Review of Non-mammalian Assays - Challenges and Potential Solutions for the Conduct and Interpretation of the Amphibian Metamorphosis Assay and the Fish Short Term Reproduction Assay

Dr. Katherine Coady - The Dow Chemical Company

Katie received a B.A. degree in 1997 from Anderson University (Anderson, IN, USA) with a major in Biology and a minor in Chemistry. She received a M.S. in Zoology/Environmental Toxicology from Michigan State University in 2000. The title of her thesis was "2,3,7,8-Tetrachlorodibenzo-p-dioxin Equivalents in Tissue Samples from Three Species in the Denver Metropolitan Area" (Advisor- John P. Giesy, Ph.D.). Katie received her Ph.D in Zoology/ Ecology, Evolutionary Biology and Behavior (Specialization in Environmental Toxicology) from Michigan State University in 2003. The title of her dissertation was "An Investigation into the Mechanism of Action of Atrazine and its Effects on

Developing Rana clamitans and Xenopus laevis" (Advisor-John P. Giesy, Ph.D.). In her professional career, Katie has been employed as an environmental consultant for ENTRIX (Okemos, MI, USA), as an Assistant Professor for Warner University (Lake Wales, FL, USA), and is currently employed at The Dow Chemical Company (Midland, MI, USA) as an Environmental Toxicologist. Katie has published peer-reviewed journal articles and given multiple presentations on endocrine research and testing with non-mammalian organisms, and she has firsthand experiences conducting the in-life fish and frog Tier 1 assays that are a part of the US EPA's Endocrine Disruptor Screening Program.

Abstract

The Amphibian Metamorphosis Assay (AMA) and the Fish Short-Term Reproduction Assay (FSTRA) are screening assays designed to detect potential endocrine activity of a test substance. These assays are included in a battery of assays in Tier 1 of USEPA's Endocrine Disruptor Screening Program. The AMA is a 21-day aquatic exposure designed to assess potential endocrine activity in the hypothalamus-pituitary-thyroid axis of developing African clawed frogs (*Xenopus leavis).* The FSTRA is a 21-day aquatic exposure designed to assess potential endocrine activity in the hypothalamus-pituitary-gonadal axis of sexually mature fathead minnows (*Pimephales promelas).* Results from these assays, in conjunction with other Tier 1 endocrine screening assays, are used to determine if further testing to assess interactions with the endocrine system is required for test substances. Based on our experience and the experience of others with these two assays, we have noted several challenges in the conduct and interpretation of the AMA and FSTRA, and our approaches are described for dealing with these challenges. Some historical control data for both the AMA and FSTRA are presented to further understand background occurrences of histopathological phenomena and variability associated with the measured endpoints in these assays.

PANEL DISCUSSANTS

Dr. Ronald Biever, Smithers Viscient

Ron has been with Smithers Viscient for 25 years working in nearly every science and business related aspect of the organization throughout his tenure. Ron started with mesocosm and large-scale field studies, and then headed up analytical services and some environmental fate and metabolism programs before becoming the Director of Ecotoxicology Services. Ron served as Vice President of North American Operations for 5 years before taking on the role of Chief Scientific Officer. While at Smithers Viscient Ron has helped customers in the agricultural, pharmaceutical and personal products industries with a wide array of regulatory science issues. Ron spent some time working for Texas Parks and Wildlife after completing his Masters degree in Fisheries Science at Texas A&M University.

Dr. Donald Stump, WIL Research

Dr. Stump earned a B.S. in toxicology from the Philadelphia College of Pharmacy and Science (1985). In addition, Dr. Stump received a Ph.D. in biochemistry from Vanderbilt University (1990) and post-doctoral training at the National Institutes of Health. He has been employed at WIL Research since 1994 and his current title is Vice President of Nonclinical Safety Science, U.S. In this role he oversees

the General Toxicology, Developmental and Reproductive Toxicology, Genetic Toxicology and Pathology departments at WIL Research. Dr. Stump has published numerous research articles, book chapters and abstracts. He has also made several presentations at regional and national meetings including meetings hosted by the American College of Toxicology, Society of Toxicology, Teratology Society, Korean Society of Nonclinical Study and the North American Congress of Clinical Toxicology. He is currently on the journal editorial board for both Birth Defects Research Part B: Developmental and Reproductive Toxicology and Congenital Anomalies. He is a Diplomate of the American Board of Toxicology (1999) and a member of the Teratology Society, the European Teratology Society, the Japanese Teratology Society, the Society of Toxicology, the Mid-Atlantic Reproduction and Teratology Society and the Japanese Society of Toxicology.

Dr. Kun (Sue) Yi, Syngenta Crop Protection

Kun Don "Sue" Yi attended Texas Christian University, where she received her Bachelor of Science in Chemistry and Biology with a minor in Art History. She received her Master of Science in Integrative Physiology with a focus on cardiovascular physiology at the University of North Texas Health Science Center in Fort Worth, TX. She completed her PhD at the University of North Texas Health Science Center in Fort Worth, TX. The major focus of her PhD dissertation was to understand the mechanisms of neuronal dysfunction in aging and stroke as well as neuroprotection mediated by estrogens and estrogen analogues. Her post-doctoral training involved assessing oxidative stress and aromatase induction due to exposure to a triaizine herbicide. During her time as junior faculty at the University of North Texas Health Science Center, she and colleagues tried to identify biomarkers to explain the racial disparities seen in various disease morbidities and mortalities, in addition to pursuing her interest in mechanisms of neuronal dysfunction in aging and disease. In 2010, she joined Syngenta Crop Protection as a toxicologist, where she is involved in mode of action studies as well as development of new crop protection chemicals.

Session II - Practical Applications of Tier 1 Data

SESSION CHAIR

Dr. Sue Marty

Dr. Sue Marty received her M.P.H. and Ph.D. degrees from the University of Michigan, specializing in the area of reproductive toxicology. She was a postdoctoral fellow at Michigan State University, where she studied the neurotoxicity of methylmercury. In 1997, she joined The Dow Chemical Company, where she is currently a Senior Toxicology Leader in the Neuroendocrine toxicology group. Dr. Marty is a diplomate of the American Board of Toxicology (D.A.B.T.) and a member of the editorial board for Birth Defects Research Part B: Developmental and Reproductive Toxicology. She is an active member of the Society of Toxicology and Teratology Society and has served on expert panels for the National Toxicology Program (NTP) and Organization for Economic Cooperation and Development (OECD). Her research interest is investigating the modes-of-action for chemical effects on the endocrine system and neurodevelopment.

A Two-Tiered-Testing Decision Tree for Assays in the USEPA-EDSP Screening Battery: Using 15 years of experience to improve screening and testing for endocrine active chemicals.

Dr. L. Earl Gray Jr. and Dr. Gerald Ankley, US Environmental Protection Agency

L. Earl Gray, Jr is a senior reproductive toxicologist in the Reproductive Toxicology Division, Endocrinology Branch at the U.S. Environmental Protection Agency (US EPA). Dr. Gray is also an Adjunct Professor at the North Carolina State University Department of Toxicology. His research is focused on how individual toxicants and mixtures induce alterations of mammalian reproductive development. Dr. Gray's research team is investigating mechanisms by which chemical exposure alter steroid hormone action during critical developmental periods that result in altered reproductive morphology and function, Mechanisms under investigation include, AR, ER, AhR and hormone synthesis inhibition mediated alterations in the reproductive system. The overall objectives are to compare 1) effects of low doses of toxicants with 2) in vivo tissue levels of the active metabolite(s), 3) determine how mixtures of chemicals with similar and different modes of action interact and to 4) identify in vivo and in vitro mechanisms of action. In their studies, pregnant animals are exposed during developmental stages and the reproductive system of the male and female offspring assessed throughout lactation, puberty, mating and, on occasion, old age. Chemicals of interest include antiandrogenic fungicides, phthalates and xenoestrogens. Currently, they are very interested in how chemicals with divergent mechanisms of action interact during sexual differentiation to determine how often synergistic effects are seen. Dr. Gray has earned 15 USEPA Scientific and Technological Achievement Awards, 2 gold medals for USEPA Service, and 7 bronze medals for USEPA Service. He has contributed to numerous peer-reviewed journal articles and has been an invited lecturer at several

national and international symposia. Dr. Gray received his Ph.D. in Zoology from North Carolina State University.

Abstract

In 1996 the Food Quality Protection and Safe Drinking Water Acts instructed the USEPA to determine "…whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects;"*. In 1998 EDSTAC, an advisory committee to EPA, recommended that EPA develop a screening battery that included mammalian and non-mammalian *in vivo* and in vitro assays to detect chemicals for estrogen, androgen and thyroid activities (EAT). The battery was intended to detect chemicals that disrupted EAT pathways via the E and A nuclear receptors, steroid hormone synthesis or disruption on hypothalamic-pituitary-gonadal function via EAT modes of action. The last 15 years since the release of the EDSTAC Final Report was published, EPA has been developing and validating the assays for screening and, as a result, a significant data base has been developed using chemicals with known EDC activities. This database enables us to review assay performance and make recommendations about 1) Interpretation of assay results with unknowns, 2) Structuring the screening battery into a "Tiered-Testing Decision Tree" with two *in vivo* "Gatekeeper" assays and, 3) Specifically tailoring Tier 2 testing using the EDC information gained from Tier 1 screening. This presentation will discuss development of the screening battery by EDSTAC, assay development and validation, how the battery detects different EAT modes of action, the strategy for detection of positives and negatives in a Tiered-Testing Decision Tree battery with "Gatekeeper" assays, why in vitro assays cannot serve as "Gatekeepers" and how the information from the screening battery can be used to enhance Tier 2 testing on a case-by-case basis. In addition, the presentation will address some of the criticisms of the screening battery, some of which are without merit, and reiterate how critical it is for laboratories executing the assays to strictly adhere to the published test guidelines for the screening assays.

Pulling it Together - Preparing for a Weight of Evidence Assessment on Endocrine Activity

Dr. Sue Marty, The Dow Chemical Company

Please see Session Chair biography above.

Abstract

The US EPA's Endocrine Disruptor Screening Program (EDSP) Tier 1 battery contains eleven assays designed to detect potential test material interactions with the estrogen, androgen and thyroid pathways. Results from these studies are used in a weight of evidence assessment to determine potential endocrine activity of a test compound and possibly provide information on the endocrine mode of action (MoA). This presentation will examine available information to be included in a weight of evidence assessment for interactions with the estrogen, androgen or thyroid pathways. The focus will involve an integration of EDSP Tier 1 results with other available toxicity information to look for patterns that may indicate a potential endocrine MoA. Federal Insecticide, Fungicide,

and Rodenticide Act (FIFRA) data requirements (40 CFR Part 158 toxicity studies) contain relevant information, which can provide valuable evidence for or against endocrine activity. Supporting evidence also may be derived from ToxCast, published data, etc. In addition, the impact of stress/systemic toxicity must be considered in the evaluation of potential endocrine activity. An information framework will be introduced that can be used for weight of evidence assessments and/or differentiating potential MOAs. This overall assessment can aid in the determination of whether further endocrine testing is needed and if so, which Tier 2 tests might be appropriate to better characterize endocrine hazards and dose-response relationships.

A Weight of Evidence Approach to Examine Endocrine Activity

Dr. Christopher Borgert, Applied Pharmacology & Toxicology, Inc.

Christopher J. Borgert, Ph.D. is President of Applied Pharmacology and Toxicology, Inc. (APT), a consulting firm that specializes in applied research in the areas of causation analysis, safety assessment and study design. He also holds a courtesy faculty appointment in the Department of Physiological Sciences, University of Florida College of Veterinary Medicine. He received a bachelor of arts from Kenyon College, Gambier, Ohio, a doctorate in Pharmacology and Therapeutics from the University of Florida College of Medicine, and completed a postdoctoral fellowship in toxicology at the University of Florida Center for Environmental and Human Toxicology. He has served on the U.S.EPA Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) as the general representative for Small Business stakeholders, has testified before Congress regarding the Endocrine Disruptor Screening Program, and has served on numerous national and international expert and peer-review panels, including the Society of Toxicology Expert Panel on Chemical Mixtures, OECD Peer-Review Panel for uterotrophic assay validation, and ICCVAM Peer-Review Panel for the BG1-Luc estrogen transcription activation assay. He is past President of the International Society of Regulatory Toxicology and Pharmacology (ISRTP), 2007-2008. His recent publications address methods for evaluating chemical mixtures in human milk, cumulative risk assessments for human exposure to drugs and chemicals, the pharmacology and toxicology of dietary supplements and interactions with drugs, and mechanistic dose-response evaluation for chemicals in human tissues, as well as conceptual and basic research papers that address the use of interaction data in mixture risk assessment and clinical medicine. He has recently contributed commentaries and editorials on the debate over conflict of interest and the peer-review process.

Abstract

A hypothesis---based weight of evidence (HB---WoE) framework was recently published [1] for data from the U.S. EPA's Tier 1 Endocrine Screening BaIery (ESB). The approach weights each experimental endpoint according to its relevance for deciding each of 8 hypothesis addressed by the ESB, and combines these WREL values with response weightings (WRES) that reflect the strength of response produced by the test chemical in each endpoint relative to positive and negative controls.. *A priori* relevance weightings (WREL) seek transparency and objectivity not assured by processes based on professional judgments alone. The positive and negative predictive value of ESB assays is unknown [2], thereby obviating quantitative WREL values, so an expert panel

of scientists from the Endocrine Policy Forum adjudicated endpoints according to 3 WREL categories. Endocrine hormones produce specific effects in target tissues and organs in animals; thus, Rank 1 includes only *in vivo* endpoints for androgen, estrogen and thyroid agonist and antagonist hypotheses, typically, the hallmark endpoints that define each hormone. Rank 1 endpoints are specific and sensitive for the hypothesis, are interpretable without other endpoints, and are rarely confounded by artifacts or non---specific activity. Rank 2 endpoints are also specific and interpretable for the hypothesis, but are less informative than Rank 1, often due to oversensitivity, inclusion of narrowly context---dependent components of the endocrine response (e.g., many *in vitro* endpoints), or confounding by non---specific activity. Rank 3 endpoints are relevant for the hypothesis, but only corroborative of Rank 1 and 2 endpoints. Rank 3 includes many apical *in vivo* endpoints that can be affected by systemic toxicity and activity other than the hypothesized hormonal activity. Although WREL rankings so derived necessarily involve professional judgment, their *a priori* derivation enhances transparency and renders WoE determinations amenable to methodological scrutiny according to basic scientific premises. The rationale for Rank 1 and 2 endpoints for the estrogen agonist hypothesis is presented as an example.

PANEL DISCUSSANTS

Patricia Bishop, People for the Ethical Treatment of Animals (PETA)

Ms. Bishop is a Research Associate at PETA, where her job duties include advocating for replacement of animal testing methods with more human-relevant, mode of action-based methods; tracking and reviewing EPA programs that require regulatory testing and providing stakeholder comments on issues regarding animal testing; and keeping abreast of developing non-animal TOX21 methods for evaluating chemical toxicity. Ms. Bishop recently co-authored scientific articles on 1) the use and acceptance of Other Scientifically Relevant Information in EPA's Endocrine Disruptor Screening Program, 2) a retrospective on animal use and regulatory testing in EPA's High Production Volume (HPV) Chemical Challenge Program, and 3) demonstration of an integrated testing strategy for identifying potential endocrine disruptors. Prior to coming to PETA, Ms. Bishop completed a thirty-year career as an environmental scientist with the State of New York. She received her B.S. of Wildlife Ecology, and M.S. of Environmental Science.

Dr. Kevin Crofton, U.S. Environmental Protection Agency

Dr. Kevin M. Crofton is the Acting Deputy Director of the National Center for Computational Toxicology of the US Environmental Protection Agency in Research Triangle Park, NC. Dr. Crofton received his Ph.D. in Toxicology from the University of North Carolina, Chapel Hill. He has been a toxicologist at EPA since 1986 and is an Adjunct Assistant Professor in the Department of Environmental and Molecular Toxicology at North Carolina State University and in the Curriculum in Toxicology, University of North Carolina at Chapel Hill. His interests include adverse outcome pathways and development of alternative testing methods for endocrine disruption. His current research efforts include development of in vitro and alternative methods for detecting thyroid disrupting chemicals. Dr. Crofton's professional activities include membership in numerous scientific

societies and participation on many professional review boards. He has presented invited lectures for a variety of government agencies in Europe, Canada, and the U.S., and for numerous professional societies and universities. In addition, he has authored or coauthored over 150 peer reviewed publications.

Dr. Ellen Mihaich, ER^2 and *Endocrine Policy Forum*

Dr. Ellen Mihaich has worked in the pesticide/chemical industry for over 23 years. She is the owner/president of Environmental and Regulatory Resources, LLC, an environmental consulting company in Durham, N.C. Prior to this position, she worked for Rhone-Poulenc and then Rhodia as an environmental toxicologist responsible for pesticide/chemical development, testing, and risk assessment. Dr. Mihaich has been involved in test guideline development and endocrine-related activities for many years. Among the many activities in this area, she is a Business and Industry Advisory Committee (BIAC) representative to the Organization for Economic Cooperation and Development (OECD) Ecological Validation Management Group for endocrine testing. She has also been an invited participant on three Intergovernmental Coordinating Committee on Validation of Alternative Methods (ICCVAM) panels on in vitro testing methods for endocrine active compounds and the use of the Frog Embryo Teratogenesis Assay Xenopus (FETAX) assay in human health assessment. She is the scientific coordinator for the Endocrine Policy Forum, a consortium of List 1 Test Order recipients and interested stakeholders. Dr. Mihaich received a B.A. from Wellesley College and both M.S. and Ph.D. degrees in environmental toxicology from Duke University, where she currently holds an adjunct appointment and teaches a graduate-level course in risk assessment. She is a past president of the Society of Environmental Toxicology and Chemistry. Dr. Mihaich is a Diplomate of the American Board of Toxicology.

Session III - Considerations in the Future of Endocrine Testing

SESSION CHAIRS

Dr. Warren Casey, National Institutes of Environmental Health Sciences (NIEHS)

Dr. Casey is currently the Acting Director of the U.S. National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), National Institutes of Environmental Health Sciences (NIEHS), and a Diplomate of the American Board of Toxicology (DABT). Prior to joining NICEATM, Dr. Casey was the Manager of the Pharmaceutical Microbiology group at Glaxo Inc. from 1994 to 1999; Head, Biomarker Development, at GlaxoWellcome, Inc., from 1999 to 2002; and a Senior Scientist, Discovery and Investigative Toxicology, at GlaxoSmithKline, Inc., from 2002 to 2009. Dr. Casey is actively involved with the Organization for Economic Cooperation and Development (OECD) and serves on several international validation management teams. Dr. Casey also serves as an Adjunct Associate Professor in the Department of Microbiology at NCSU. Dr. Casey received his undergraduate degree in biochemistry and his Ph.D. in microbiology from North Carolina State University (NCSU).

Dr. Jack Fowle, U.S. Environmental Protection Agency (retired)

Dr. John R. "Jack" Fowle III is an independent consultant specializing advising clients about the use of science to inform decisions regarding environmental risk and in the development and use of alternatives for animal testing. Prior to 2012 he was the Deputy Director of the U.S. Environmental Protection Agency's (EPA) Health Effects Division in the Office of Pesticide Programs (OPP) in Washington, DC where he was responsible for directing the health risk assessment activities supporting the re-registration of existing pesticides and helping to manage the integration of new toxicological approaches into OPP's human health risk assessments, including coordination of the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) activities across EPA. Before coming to OPP he was Director of EPA's Neurotoxicology Division at the National Health and Environmental Effects Research Lab (NHEERL) in Research Triangle Park, NC. There he implemented programs to develop alternatives to animal approaches. He also served as Assistant Laboratory Director in NHEERL managing the research program on commercial chemicals across the both health and ecological effects research divisions. A large part of his work was to develop approaches to support the screening and prioritization of chemicals and the enhanced interpretation of data using QSAR and alternative animal tests. He has served as Deputy Director of EPA's Science Advisory Board and as the Science Advisor to U.S. Senator Daniel Patrick Moynihan. He received both his baccalaureate and doctoral degrees in genetics from George Washington University in Washington, DC.

Dr. Richard Becker, American Chemistry Council

Richard A. Becker earned a B.A. in Chemistry from Swarthmore College and a Ph.D. in Pharmacology and Toxicology from the University of California, received post-doctoral training at the University of Toronto and the International Agency for Research on Cancer, and is a Diplomate of the American Board of Toxicology. He was a toxicology study director for NTP and NCI sponsored toxicity studies at SRI International (1985-1987), and then served as a senior scientist with the State of California from 1987 to 1999. His experience in California government included appointments to increasingly important technical and scientific management positions, beginning in Department of Toxic Substances Control, rising first to Deputy Director of Scientific Affairs in the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA), and subsequently to Director of OEHHA by appointment of Governor Wilson. In these positions, he initially conducted and then managed hazard evaluations, exposure assessments and risk characterizations to determine health and environmental threats posed by the exposures to hazardous substances in the environment. Dr. Becker joined the American Chemistry Council in 1999, where he continues to serve as the organization's senior toxicologist in addressing emerging health risk science issues, including advanced risk assessment techniques, biomonitoring, sensitive subpopulations, endocrine screening and testing and alternative test methods.

EPA ToxCast HTS Assays and Prediction Models for Estrogen, Androgen, Thyroid and Steroidogenesis Pathways

Dr. David Dix, US Environmental Protection Agency, NCCT

Dr. David J. Dix is Acting Director of the U.S. Environmental Protection Agency's National Center for Computational Toxicology (NCCT), at Research Triangle Park, NC, USA, where he is leading the development of high throughput decision support tools for screening and assessing chemical exposure, hazard and risk. Prior to Acting Director, Dr. Dix was the NCCT Deputy Director and a Research Biologist conducting research in reproductive, genomic and computational toxicology at EPA. Dr. Dix is an adjunct Associate Professor in the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill. He earned his undergraduate degree in Biological Sciences from the University of Illinois at Chicago, a Ph.D. in Physiology from Rush University in Chicago, and completed postdoctoral training at the U.S. National Institute of Environmental Health Sciences. He has published over 115 articles, reviews, reports and book chapters, serves on several Editorial Boards, and given numerous national and international presentations on EPA research.

Abstract

EPA's endocrine disruptor screening program (EDSP) is currently finalizing the inter-laboratory validation of test protocols to be used to determine endocrine-related effects caused by potential endocrine disruptors; prioritizing and selecting additional chemicals to undergo screening to determine potential for endocrine disruption; issuing orders to conduct testing for additional chemicals; and reviewing test data submitted and conducting weight of evidence (WoE) evaluations to determine potential interactions with endocrine systems, and whether a chemical warrants

further testing for endocrine effects. In addition, EPA is evaluating endocrine-relevant high-throughput screening (HTS) assays to increase coverage for endocrine toxicity pathways and dramatically increase testing efficiency. The EDSP is coordinating and collaborating with EPA's Office of Research and Development (ORD) to identify computational toxicology-based approaches for chemical prioritization and to develop a more efficient approach to assess a chemical's potential to interact with the estrogen, androgen, thyroid and steriodogenesis systems. The ToxCast research project is using rapid, automated chemical tests (i.e., HTS) and computational modeling for predicting endocrine disruption potential, and prioritizing chemicals for the EDSP Tier 1 screening battery. ToxCast is evaluating thousands of chemicals in HTS assays, and these results are being published along with predictions for interactions with endocrine systems. ToxCast chemical screening methods could ultimately replace the current EDSP Tier 1 Screening Battery, increasing speed and efficiency, and reducing animal use. The ExpoCast research project is developing computational models with capacity to rapidly forecast human exposure for all of the 8000 ToxCast/Tox21 chemicals. ExpoCast model predictions are based on chemical properties and use information from ACToR and other databases. ExpoCast data and exposure predictions will be published, and incorporated into predictions of endocrine disruption risk. The EPA Chemical Safety for Sustainability or CSS Dashboard accesses information on chemical exposure, hazard, risk, and sustainability; integrating diverse sources of information and supporting problem-driven analytics. The CSS Dashboard will be a web-accessible portal for current ToxCast, Tox21 and ExpoCast data. Public release of the beta version of the Dashboard is scheduled for September 2013, with ToxCast HTS data on 1800 chemicals in 650 high-throughput screening assays, Tox21 HTS data on 8,000 chemicals, and ExpoCast exposure predictions for these same 8,000 Tox21 chemicals. In the near term, these computational toxicology tools will enable EPA to more efficiently prioritize chemicals for screening and increase efficiency in identifying chemicals with the potential to disrupt the endocrine system. In this fashion the EPA is continuing the multi-year transition away from the traditional assays used in the EDSP through validation and use of computational toxicology and other higher throughput methods. *This abstract does not represent EPA policy.*

Tier 1 and Done: Developing *in vitro* Cell-based Assays of Endocrine Pathways Sufficient by Themselves for 21st Century Risk Assessment

Dr. Mel Andersen, The Hamner Institutes for Health Sciences

Mel is the Charles Hamner Distinguished Fellow and the Associate Director of the Institute of Chemical Safety Sciences at The Hamner Institutes for Health Research, Research Triangle Park, NC. Over a 40 plus year toxicology career, he worked in the federal government (US Navy, Department of Defense and EPA), private industry (ICF Kaiser) and academia (Colorado State University). His career work in pharmacokinetics and pharmacodynamics emphasized the importance of computational modeling approaches for understanding dose response relationships with environmental chemicals. Increasingly, his research at The Hamner focuses on implementing the in vitro toxicity testing approaches outlined in the 2007 US National Academy of Sciences report, "Toxicity Testing in the 21st Century: A Vision and A Strategy" through the use of case studies. You can find the current Hamner

programs related to toxicity pathways and human health safety assessments with these case studies on The Hamner web site (www.thehamner.org/tt21c).

Abstract

The 2007 NAS report, "Toxicity Testing in the 21st Century: A Vision and A Strategy", proposed conducting future safety assessments for environmental agents by developing data from a suite of in vitro assays designed to assess perturbations of 'toxicity pathways' in human cells or cell lines and be amenable to computational pathway modeling in intact cells to assess dose-response relationships. Our Hamner research program with a cellular estrogen-pathway develops targeted *in vitro* assays for prototype estrogenic compounds in uterine cells/tissues, refines interpretive bioinformatic tools to map estrogen pathway circuitry in these cells, and creates computational pathway models for the dose-response relationships for pathway perturbations. The overall goal is to provide 'validated' *in vitro* assays for estrogen pathways in human uterine cells and the necessary dose-response modeling modalities so that dose-response information from the 'validated' *in vitro* assays will be considered sufficient for conducting safety assessments with estrogenic compounds without progressing to toxicity studies in intact animals; thus the concept – "Tier 1 and Done". In this usage, Tier 1 implies well-designed, 'validated' *in vitro* assays rather than referring explicitly to the existing Tier 1 battery in US EPA Endocrine Disruptor Screening Program (EDSP). This talk will outline our on-going studies with Ishikawa cells, a human uterine adenocarcinoma cell line; enumerate the data streams used to map the estrogen signaling pathway for compounds that selectively activate ESR1, ESR2, GPER, and membrane forms of ESR1; describe the initial structure of the multi-receptor, computational systems biology pathway models; and discuss the risk/safety assessment directions provided by detailed understanding of pathway architecture. In a more generic sense, these studies on the uterine cell E2-signaling pathway should optimize the generic pathway-related process for chemical safety assessment. Work on subsequent pathways should become streamlined and less costly, thereby accelerating implementation of the recommendations of the 2007 report.

Mapping the Human Toxome by Systems Toxicology - Using ED as a Proof of Concept

Dr. Thomas Hartung, Center for Alternatives to Animal Testing, Johns Hopkins

Thomas Hartung, MD PhD, is Professor of Toxicology (Chair for Evidence-based Toxicology), Pharmacology, Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore, and University of Konstanz, Germany; he also is Director of their Centers for Alternatives to Animal Testing (CAAT, http://caat.jhsph.edu) with the portal AltWeb (http://altweb.jhsph.edu). CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration (http://www.ebtox.com/) and the industry refinement working group. As PI, he heads the Human Toxome project funded as an NIH Transformative Research Grant. He is the former Head of the European Center for the Validation of Alternative Methods (ECVAM), Ispra, Italy. He has authored more than 370 scientific publications.

Abstract

The National Research Council report from 2007 "Toxicity Testing in the 21st Century: A vision and a strategy" has created an atmosphere of departure in the US. It suggests moving away from traditional (animal) testing to modern technologies based on pathways of toxicity. These pathways of toxicity could be modeled in relatively simple cell tests, which can be run by robots. The goal is to develop a public database for such pathways, the Human Toxome, to enable scientific collaboration and exchange.

Tox-21c suggests moving to a new resolution, i.e. pathways of toxicity. The problem is that the respective science is only emerging. What will be needed is the Human Toxome as the comprehensive pathway list, an annotation of cell types, species, toxicant classes and hazards to these pathways, an integration of information in systems toxicology approaches, the in-vitro-in-vivo-extrapolation by reversed dosimetry and finally making sense of the data, most probably in a probabilistic way. The NIH is funding since September 2011 by a transformative research grant The Human Toxome project led by CAAT. The project involves US EPA ToxCast, the Hamner Institute, Agilent and several members of the Tox-21c panel. The new approach is shaped around pro-estrogenic endocrine disruption as a test case.

Early on, the need for quality assurance for the new approaches as a sparring partner for their development and implementation has been noted. The Evidence-based Toxicology Collaboration (EBTC) was created in the US and Europe in 2011 and 2012, respectively. This collaboration of representatives from all stakeholder groups aims to develop tools of Evidence-based Medicine for toxicology, with the secretariat run by CAAT. All together, Tox-21c and its implementation activities including the Human Toxome and the EBTC promise a credible approach to revamp regulatory toxicology.

The Future of Endocrine Screening: An Animal Welfare Perspective

Dr. Catherine Willett, Humane Society of the United States

Dr. Willett obtained her MS and PhD in Genetics from the University of California, Davis, studying the genetics and biochemistry of gene regulation in yeast. In her post-doctoral work at MIT, Dr. Willett initiated the study of the zebrafish immune system, work that contributed to the understanding that the fish immune system shares many cellular, molecular and developmental similarities with the mammalian immune system. As a Senior Scientist at Phylonix Pharmaceuticals, Dr. Willett was Principle Investigator on several NIH and NSF-sponsored projects in the areas of angiogenesis, developmental toxicity, hepatic toxicity, developmental neurotoxicity, and endocrine disruption.

Since 2006, Dr. Willett has focused on the science, policy and regulatory aspects of replacing animals as the basis of chemical safety assessment, first as Science Policy Advisor for People for the Ethical Treatment of Animals, and more recently as the Director of Regulatory Toxicology, Risk Assessment and Alternatives at the Humane Society of the United States. This effort involves working with regulatory agencies, scientists and policy makers in the US and internationally, to facilitate the development and implementation of methods that reduce or replace animals in chemical assessment

processes. As coordinator of the Human Toxicology Project Consortium, Dr. Willett has recently become involved in promoting toxicity pathways as an organizing principle for chemical safety assessment and presented at this topic at several international conferences in 2012. Dr. Willett is a member of SOT, has been on the board of the International QSAR Foundation and is on the Scientific Advisory Board of the Institute of In Vitro Sciences.

Abstract

The current, two-tiered structure of US EPA's EDSP is resource, labor and animal-intensive: the 11 assays that comprise the Tier 1 use more than 570 animals per assessment, and the Tier 2 tests assess dose-response effects in multiple species will use thousands more. In an effort to increase efficiency for the data-rich chemicals in Phase I, EPA was directed to accept existing "other scientifically relevant information" to the "greatest extent possible;" however, as practiced, this resulted in only a modest reduction in new data being requested. EPA's efforts to introduce ToxCast assays as a prioritization tool are to be commended and supported; however, that approach alone will do little to improve the overall efficiency of the screening program other than to make sure the chemicals that are most likely to be active get tested first. Measures are also needed to enhance the efficiency of the entire screening program. Other issues with the current design also need addressing, including: insufficient opportunity for chemically-relevant tailoring; generation of a large amount of data, only some of which may have regulatory use; a lack of predictivity (empirical data from one chemical does not enhance the prediction of future chemicals); coverage of only a subset of "endocrine" effects. The structure of the EDSP could be improved in stages – the first being a more refined tiering system that allows increased opportunity for chemical-specific assessment In such a system, the initial tier takes into account all existing information, including phsysicochemical, the second tier assesses potential mechanisms of action and is followed by tests that address potential effects in more complex systems or on multiple modes of action, and lastly by tests that address adverse outcome and dose-response. Weight-of-evidence with clearly articulated criteria is applied at each tier. These criteria define positive and negative cut-offs at the outset for each test and each tier and the results are then used to design the strategy for further testing. In this way, testing is streamlined and the information generated is more likely to be of regulatory relevance for the chemical being tested. This approach could be taken with no or little new test design or validation. A second phase of improving the EDSP design involves a shift to pathway-based approaches. Several projects that are developing the elements of this shift are underway, including EPA's estrogen receptor activation decision framework, endocrine-relevant ToxCast assays, the development of an estrogen receptor adverse-outcome (or mechanism of action) pathway at the Hamner Institute, and several ongoing projects being coordinated through the OECD. These projects require further development and coordination, but together will form the basis of an integrated testing strategy that will more efficiently provide regulatory information, effectively link chemical mechanism with adverse outcome and create a predictive paradigm for endocrine assessment.

Road Map for Building Scientific Confidence in HTP Assays

Dr. David Geter, Bayer CropScience

David received his B.S. in Biology (1995) from the University of Louisiana, M.S. in Zoology (1997) from Oklahoma State University, and Ph.D. in Biological Science (2001) from the University of Southern Miss. Over the past decade he has worked in both the Federal Government and Chemical Industry examining environmental and human health effects of chemical exposure. From '01 - '06, his primary area of responsibility was examining the effects of drinking water disinfection by-products in acute and chronic rodent studies at the US Environmental Protection Agency in RTP. Additionally, he was an Adjunct Professor at Mount Olive College during this time. From '06 to May '12, he worked as a toxicologist at The Dow Chemical Company where his primary focus was on molecular, genetic, and endocrine toxicology. From May '12 to the present, he has worked at Bayer CropScience as a Regulatory Toxicologist in Human Safety.

Dr. Lisa Ortego, Bayer CropScience

Lisa S. Ortego, Ph.D., DABT, is an ecotoxicologist with Bayer CropScience. She holds a Ph.D. in pharmacology and toxicology from the University of Mississippi and is certified by the American Board of Toxicology. Dr. Ortego has worked in the private sector since 1995. She has a leadership role in her company and in industry working in the endocrine issues area. She chairs the technical working group of the Endocrine Policy Forum, a consortium to address needs with respect to regulatory, policy and technical issues.

Abstract

High throughput (HTP) assays are the future of endocrine screening and testing. However, HTP assays typically undergo minimal validation. As outlined in the National Research Council (NRC) report "Toxicology Testing in the 21st Century", the path forward calls for the increased use of HTP assays within chemical safety evaluations. This is driven by the large number of chemicals in commercial use and the desire to refine, reduce, and replace animal testing. However, to achieve this goal, HTP assays need to be better validated. Two current efforts providing guidance for HTP-like methods are from the Institute of Medicine's Biomarker Framework and the OECD QSAR Validation Strategy. These suggest that HTP assays provide: 1) scientific and regulatory purpose for the assay, 2) a detailed protocol complete with positive and negative controls, 3) the limitations of the method in relation to reliability and reproducibility, 4) the chemical domain of applicability, and 5) *a priori* criterion for interpretation. Furthermore, prediction models should be developed and evaluated using appropriate training sets with data criteria, filters, and algorithms disseminated to assure 100% transparency. The end result of these steps is communication through peer review publications, independent science advisory boards, and/or systematic collaborative review. If adopted by the toxicology community, this framework approach would provide a validation strategy resulting in the necessary scientific confidence to accept and embrace HTP assays and prediction models for regulatory applications.

Designing the Next Generation of Sustainable Chemicals

Thaddeus Schug, National Institutes of Environmental Health Sciences (NIEHS)

Thaddeus (Thad) Schug, Ph.D., is a program administrator in the Cellular, Organs, and Systems Pathobiology Branch in the extramural division of NIEHS where he is involved with programs in the scientific areas of male and female reproduction, metabolism, the development and disruption of the endocrine systems, and nanotechnology. He also has interest in projects associated with green chemistry. Thad received his doctorate in nutrition and biomedical sciences from Cornell University. His graduate work focused on the relationships between nuclear hormone receptor activation and various forms of cancer. Thad conducted his postdoctoral studies at the National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS). At NIH, he investigated the sirtuin family of genes, which are involved in the aging process, homeostasis, metabolism, and inflammation.

Abstract

A central goal of green chemistry is to avoid hazard in the design of new chemicals. This objective is best achieved when information about a chemical's potential hazardous effects is obtained as early in the design process as feasible. Endocrine disruption is a type of hazard that to date has been inadequately addressed by both industrial and regulatory science. To aid chemists in avoiding this hazard, we propose an endocrine disruption testing protocol for use by chemists in the design of new chemicals. The Tiered Protocol for Endocrine Disruption

(TiPED) has been created under the oversight of a scientific advisory committee composed of leading representatives from both green chemistry and the environmental health sciences. TiPED is conceived as a tool for new chemical design, thus it starts with a chemist theoretically at "the drawing board." It consists of five testing tiers ranging from broad in silico evaluation up through specific cell- and whole organism-based assays. To be effective at detecting endocrine disruption, a testing protocol must be able to measure potential hormone-like or hormone-inhibiting effects of chemicals, as well as the many possible interactions and signaling sequellae such chemicals may have with cell-based receptors. Accordingly, we have designed this protocol to broadly interrogate the endocrine system. The proposed protocol will not detect all possible mechanisms of endocrine disruption, because scientific understanding of these phenomena is advancing rapidly. To ensure that the protocol remains current, we have established a plan for incorporating new assays into the protocol as the science advances. In this paper we present the principles that should guide the science of testing new chemicals for endocrine disruption, as well as principles by which to evaluate individual assays for applicability, and laboratories for reliability. In a 'proof-of-principle' test, we ran 6 endocrine disrupting chemicals (EDCs) that act via different endocrinological mechanisms through the protocol using published literature. Each was identified as endocrine active by one or more tiers. We believe that this voluntary testing protocol will be a dynamic tool to facilitate efficient and early identification of potentially problematic chemicals, while ultimately reducing the risks to public health.

Session IV - Participant Discussion

Dr. James C. Lamb, Exponent, Inc., Opening Remarks

Jim Lamb has more than 30 years of experience specializing in toxicology, risk assessment, and regulatory policy. He has worked on hormonally active agents in the environment ("endocrine disruptors") since 1976 when he joined the National Institute of Environmental Health Sciences (after getting his Ph.D. at the University of North Carolina). Jim moved to the National Toxicology Program, then to EPA as the Special Assistant for Pesticides in the Office of Pesticides and Toxic Substances. He has been a consultant in this area for over 25 years and is currently the Center Director of Exponent's Toxicology and Mechanistic Biology Center.

Jim has served on numerous scientific panels for government and private organizations. A few of the organizations that he has served include: several National Academy of Sciences Committees, the U.S. Delegation to the Organization for Economic Cooperation and Development (OECD), and the International Life Sciences Institute (ILSI). He is now President of the Academy of Toxicological Sciences. He was honored by the SOT's Mid-Atlantic Society of Toxicology as their 2011 Ambassador of Toxicology.

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (TERA), Facilitator

Michael Dourson founded Toxicology Excellence for Risk Assessment (TERA), a nonprofit corporation with a mission to protect public health. TERA develops partnerships among government, industry and other interested groups to address risk assessments of high visibility. Prior to TERA, Michael worked 15 years for EPA, holding several leadership roles and winning awards for joint efforts, such as the creation of EPA's Integrated Risk Information System (IRIS). In 2003, he was selected for the Society of Toxicology's Arnold J. Lehman award for major contributions that improve the scientific basis of risk assessment. In 2007, he was elected as a Fellow of the Academy of Toxicological Sciences. In 2009, he was selected for the International Society of Regulatory Toxicology and Pharmacology's International Achievement Award in recognition of his outstanding contributions nationally and internationally to the advancement of regulatory science. In 2009, he was also selected as a Fellow for the Society for Risk Analysis for substantial achievement in science relating to risk analysis and service to SRA. Michael has co-published more than 100 papers on risk assessment methods, including methods for assessing risk in sensitive subgroups, on use of animal and human data in the assessment of risk, or on assessments for specific chemicals. He has also co-authored well over 100 government risk assessment documents, made over 100 invited presentations, and chaired well over 100 sessions at scientific meetings and independent peer reviews. He has been elected to multiple officer positions in the American Board of Toxicology, the Society of Toxicology (SOT), and the Society for Risk Analysis.

This page intentionally blank

Registered Attendees

This page intentionally blank

List of In-Person Attendees

Dr. Mohammad Akbarsha
Mahatma Gandhi-Doerenkamp Center (MGDC) for Alternatives
director@mgdccloud.org

Dr. Melvin Andersen
The Hamner Institutes for Health Sciences
mandersen@thehamner.org

Mr. John Aufderheide
ABC Laboratories
mooreb@abclabs.com

Dr. William Baldwin
Clemson University; Biological Sciences
baldwin@clemson.edu

Dr. Marcy Banton
LyondellBasell
marcy.banton@lyondellbasell.com

Dr. Richard Becker
American Chemistry Council
rick_becker@americanchemistry.com

Dr. Tom Beidler
Syngenta Crop Protection
tom.beidler@syngenta.com

Dr. Karin Bentley
DuPont Crop Protection
karin.s.bentley-1@usa.dupont.com

Mr. Peter Beyrouty
Gowan
pbeyrouty@gowanco.com

Dr. Rachelle Bienstock
EPA/Lockheed Martin Contractor -NCCT
bienstock.rachelle@epa.gov

Mr. Ronald Biever
Smithers Viscient
rbiever@smithers.com

Ms. Patricia Bishop
People for the Ethical Treatment of Animals
PatriciaB@peta.org

Dr. Christopher Borgert
University of Florida / Applied Pharmacology & Toxicology, Inc.
cborgert@ufl.edu

Dr. Susan Borghoff
ILS, Inc.
sborghoff@ils-inc.com

Dr. Mounir Bouhifd
CAAT - Johns Hopkins School of Public Health
mbouhifd@jhsph.edu

Dr. Amy Brix
EPL/NTP
brix@niehs.nih.gov

Dr. Maureen Bunger
Cellular Dynamics International
mbunger@cellulardynamics.com

Mr. Jon Busch
American Chemistry Council
jon_busch@americanchemistry.com

Ms. Jessica Cain
Duke University
jessica.cain@duke.edu

Mr. Jon Cartlidge
Battelle
jon.cartlidge@gmail.com

Dr. Warren Casey
NIEHS/NTP
warren.casey@nih.gov

Mr. Kevin Causey
ILS
kcausey@ils-inc.com

Dr. Xiaoqing Chang
NIEHS
changX@niehs.nih.gov

Dr. Katherine Coady
The Dow Chemical Company
kcoady@dow.com

Dr. Pragati Coder
WIL Research
pragati.coder@wilresearch.com

Dr. Lydia Cox
Nichino America Inc.
lcox@nichino.net

Dr. Kevin Crofton
US EPA
crofton.kevin@epa.gov

Dr. Yoshihito Deguchi
Sumitomo Chemical America, Inc.
ydeguchi@sumichem.com

Mr. Matt Dent
Unilever Safety and Environmental Assurance Centre
matthew.dent@unilever.com

Dr. James Deyo
Eastman Chemical Company
deyo@eastman.com

Dr. David Dix
US EPA
dix.david@epa.gov

Dr. Darlene Dixon
NIEHS/NTP
dixon@niehs.nih.gov

Dr. Vivian Doelling
Integrated Systems Analysis
vdoelling@ils-inc.com

Dr. Michael Dourson
Toxicology Excellence For Risk Assessment (TERA)
dourson@tera.org

Mr. Jack (Jay) Early
CSS-Dynamac
Jearly@dynamac.com

Dr. Willem Faber
WFTC, LLC
wfaber@msn.com

Dr. Paul Foster
NTP-NIEHS
foster2@niehs.nih.gov

Dr. Jack Fowle
Self Employed
jackfowle@aol.com

Dr. Edward Frizell
Battelle Memorial Institute
FrizellE@Battelle.org

Dr. Xiaohua Gao
NTP, NIEHS/NIH
gaox3@niehs.nih.gov

Dr. Dave Geter
Bayer CropScience
david.geter@bayer.com

Dr. Gautam Kumar Ginjupalli
Clemson University
gautamginjupalli@yahoo.co.in

Dr. Amber Goetz
Syngenta Crop Protection
amber.goetz@syngenta.com

Dr. Elliot Gordon
for: Makhteshim Agan of North America, Inc.
SoundScience@comcast.net

Dr. Leon Earl Gray, Jr.
EPA, ORD, NHEERL, TAD, RTB
gray.earl@epa.gov

Dr. Richard Guinn
Eastman Chemical Company
rguinn@eastman.com

Mr. Bill Gulledge
American Chemistry Council
bill_gulledge@americanchemistry.com

Mr. Ephi Gur
LSR Associates Inc.
ephi.gur@LSR-Associates.com

Dr. Nina Hallmark
ExxonMobil
nina.hallmark@exxonmobil.com

Mr. Larry Hammond
2,4-D Task Force
lhammond@indy.rr.com

Dr. Thomas Hartung
Johns Hopkins University
thartung@jhsph.edu

Ms. Brit'ny Hawkins
Duke Student
bjh39@duke.edu

Mrs. Joan Hedge
USEPA
hedge.joan@epa.gov

Dr. Jerrold (Jerry) Heindel
NIEHS/DERT
heindelj@niehs.nih.gov

Dr. Frederick Hess
BASF Corporation
frederick.hess@basf.com

Mr. Steve Hicks
ABC Laboratories
mooreb@abclabs.com

Dr. Kimberly Hodge-Bell
Monsanto Company
kimberly.c.hodge-bell@monsanto.com

Dr. Chris Hofelt
BASF Corp
chris.hofelt@basf.com

Ms. Katie Holmes
BASF
catherine.holmes@basf.com

Dr. Keith Houck
US EPA
houck.keith@epa.gov

Dr. Hiroyuki Iwai
Daikin Industries, Ltd.
hiroyuki.iwai@daikin.co.jp

Mr. Mark Jaber
Wildlife International
mjaber@wildlifeinternational.com

Mr. Paul Jean
Dow Corning Corporation
paul.a.jean@dowcorning.com

Dr. Brett Jones
Integrated Laboratory Systems Inc.
jonesbr2@niehs.nih.gov

Dr. Daland Juberg
Dow AgroSciences
drjuberg@dow.com

Dr. David Kossor
Eastman Chemical Co
dkossor@eastman.com

Mr. Oliver Kroner
Toxicology Excellence For Risk Assessment (TERA)
kroner@tera.org

Dr. Hank Krueger
Wildlife International
hkrueger@wildlifeinternational.com

Dr. Francis Kruszewski
American Cleaning Institute
fkruszewski@cleaninginstitute.org

Dr. James Lamb
Exponent, Inc.
jlamb@comcast.net

Dr. Edward Lampert
Lampert & Associates
lampert@lampert-japan.com

Dr. Caroline Le Sommer
The Hamner Institutes
clesommer@thehamner.org

Ms. Monica Linnenbrink
Environmental Protection Agency
linnenbrink.monica@epa.gov

Ms. Renee Martin
Analytical BioChemistry Laboratories (ABC), Inc.
martinrh@abclabs.com

Dr. Sue Marty
The Dow Chemical Company
mmarty@dow.com

Dr. Mary McBride
Agilent Technologies
mary_mcbride@agilent.com

Dr. Patricia McClellan-Green
North Carolina State University
pdmcclel@ncsu.edu

Dr. Ellen Mihaich
ER2
emihaich@nc.rr.com

Dr. David Monson
Battelle
monsonk@battelle.org

Dr. Glenda Moser
ILS
glendamoser@ils-inc.com

Mr. Syed Ahmed Mustafa
CeeTox
smustafa@ceetox.com

Dr. Takayuki Nakamura
Daikin Industries, Ltd.
takayuki.nakamura@daikin.co.jp

Ms. Barbara Neal
Exponent
bneal@exponent.com

Ms. Kim Newton
Clemson University Institute of
Environmental Toxicology
kimn@clemson.edu

Dr. Emmett OBrien
Eastman
eobrien@eastman.com

Dr. John OConnor
DuPont
john.c.oconnor@dupont.com

Dr. Lisa Ortego
Bayer CropScience
lisa.ortego@bayer.com

Dr. Thomas Osimitz
Science Strategies, LLC
tom@sciencestrategies.com

Dr. Robert Parker
Huntingdon Life Sciences
parkerr@princeton.huntingdon.com

Dr. George Parker
WIL Research
george.parker@wilresearch.com

Ms. Jacqueline Patterson
Toxicology Excellence For Risk Assessment
(TERA)
patterson@tera.org

Dr. Katie Paul
US Environmental Protection Agency
Paul.Katie@epa.gov

Mr. Terry Quill
Quill Law Group LLC
terryquill54@comcast.net

Dr. Fred Reitman
Shell
fred.reitman@shell.com

Dr. Amera Remick
WIL Research
amera.remick@wilresearch.com

Mr. Jon Rhodes
Analytical BioChemistry Laboratories (ABC),
Inc.
rhodesj@abclabs.com

Dr. Brandy Riffle
ORISE and US EPA
riffle.brandy@epa.gov

Dr. Lori Rinckel
ILS / NICEATM
lori.rinckel@nih.gov

Ms. Kathleen Roberts
B&C Consortia Management L.L.C.
kroberts@bc-cm.com

Mr. Mike Schofield
MCPA Task Force Three
cmschofield@msn.com

Dr. Thaddeus Schug
NIEHS/DERT
schug2@niehs.nih.gov

Dr. Tessa Scown
DuPont Crop Protection
tessa.scown@usa.dupont.com

Ms. Namrata Sengupta
Clemson University
namrata.sen.g@gmail.com

Dr. Valerie Shultz
Arkema
valerie.shultz@arkema.com

Mrs. Hanna Silberberg
ICL-IP America, Inc
hanna.silberberg@icl-ipa.com

Ms. Carol Sloan
RTI International
cdssm@earthlink.net

Ms. Terri Spanogle
Cheminova, Inc.
terri.spanogle@cheminova.com

Mr. Tim Springer
Wildlife International
tspringe@wildlifeinternational.com

Dr. Laurie Staska
Integrated Laboratory Systems
lstaska@ils-inc.com

Ms. Jane Staveley
Exponent, Inc
jstaveley@exponent.com

Dr. William Stokes
Kelly Services Inc. at NIEHS
stokes@niehs.nih.gov

Dr. Scott Studenberg
CSS-Dynamac
sstudenberg@css-dynamac.com

Dr. Donald Stump
WIL Research
donald.stump@wilresearch.com

Dr. Clare Thorp
CropLife America
cthorp@croplifeamerica.org

Dr. Raymond Tice
NIEHS
tice@niehs.nih.gov

Dr. Abraham Tobia
US FDA/ CVM
abraham.tobia@fda.hhs.gov

Dr. Colleen Toole
CeeTox
ctoole@ceetox.com

Dr. Maria Trainer
CropLife Canada
trainer@croplife.ca

Dr. Katie Turner
RTI International
kturner@rti.org

Dr. Glen Van Der Kraak
University of Guelph
gvanderk@uoguelph.ca

Dr. John Vandenbergh
N.C. State University
vandenbergh@ncsu.edu

Dr. Kris Venkatesh
Makhteshim Agan of North America
kvenkatesh@manainc.com

Dr. Michael Viana
CSS-Dynamac
mviana@dynamac.com

Dr. Michael Wade
Health Canada
Mike.Wade@hc-sc.gc.ca

Dr. Robbie Waites
SABIC
Robbie.Waites@sabic-ip.com

Dr. Jason Walraven
Merial Limited, A Sanofi Company
jason.walraven@merial.com

Dr. Catherine Willett
The Humane Society of the United States
kwillett@humanesociety.org

Ms. Xinyu Yang
Duke University
xy20@duke.edu

Dr. Kun Yi
Syngenta Crop Protection
sue.yi@syngenta.com

Dr. Leah Zorrilla
Integrated Laboratory Systems, Inc
lzorrilla@ils-inc.com

List of Webinar Participants

Dr. Heather Alger
The Pew Charitable Trusts
halger@pewtrusts.org

Dr. Dan Arrieta
Chevron Phillips Chemical Company
arriede@cpchem.com

Dr. Felix Ayala-Fierro
Henkel
felix.ayala-fierro@henkel.com

Dr. Ambuja Bale
US EPA
bale.ambuja@epa.gov

Mr. Craig Barker
CEFIC
cba@cefic.be

Dr. Nancy Beck
American Chemistry Council
nancy_beck@americanchemistry.com

Dr. Steven Bennett
Consumer Specialty Products Association
sbennett@cspa.org

Mr. Scott Boito
Eastman Chemical Co
sboito@eastman.com

Dr. John Brausch
BASF Corporation
john.brausch@basf.com

Dr. Patience Browne
US EPA
browne.patience@epa.gov

Dr. Annie Buard
Solvay
annie.buard2@solvay.com

Dr. Stuart Cagen
Shell Health
stuart.cagen@shell.com

Dr. Sharan Campleman
EPRI
scampleman@epri.com

Dr. Kent Carlson
U.S. CPSC
kcarlson@cpsc.gov

Ms. Patricia Ceger
Integrated Laboratory Systems, Inc.
ceger@niehs.nih.gov

Ms. Stefanie Cheung
BASF Canada Inc.
stefanie.cheung@basf.com

Dr. Amy Clippinger
PETA
amyjc@People for the Ethical Treatment of Animals.org

Ms. Kaycee Cole
NYS DOH
kvc02@health.state.ny.us

Dr. Corinne Cudicini
Solvay
corinne.cudicini@solvay.com

Dr. Zhichao Dang
RIVM
zhichao.dang@rivm.nl

Dr. Raymond David
BASF Corp
raymond.david@basf.com

Dr. Will Davies
LSR Associates Ltd
will.davies@lsr-associates.com

Dr. Richard Davis
ToxSolutions
Rick@ToxSolutions.com

Mr. Jeffrey Davis
Integrated Laboratory Systems, Inc
jdavis@ils-inc.com

Dr. Joseph Dulka
DuPont Corporate
joseph.j.dulka@dupont.com

Dr. Britt Erickson
Chemical & Engineering News
B_erickson@acs.org

Dr. Penelope Fenner-Crisp
Independent Consultant
pfennercrisp@aol.com

Mr. Robert Fensterheim
RegNet/IRIS Forum
rfensterheim@regnet.com

Dr. Suzanne Fitzpatrick
CFSAN/FDA
suzanne.fitzpatrick@fda.hhs.gov

Dr. Jefferson Fowles
Tox-Logic Consulting LLC
tox-logic@hotmail.com

Dr. Sarah Gallagher
US EPA
sarahsgallagher@gmail.com

Ms. Megan Gaughan
Stepan Company
mgaughan@stepan.com

Dr. Helen Goeden
Minnesota Department of Health
helen.goeden@state.mn.us

Dr. Paul Hanlon
Abbott Nutrition
paul.hanlon@abbott.com

Dr. Sophie Jia
Chevron Phillips Chemical Company
jiasz@cpchem.com

Dr. Lela Jovanovich
Stepan Co.
ljovanovich@stepan.com

Dr. Michael Kaplan
A. Michael Kaplan & Associates, LLC
amkaplan1@comcast.net

Dr. Kevin Keane
Consultant in Toxicologic Pathology
kevin.keane@mac.com

Dr. Janet Kester
NewFields
jkester@newfields.com

Dr. Moazzam Khan
Health Canada
moazzam.khan@hc-sc.gc.ca

Ms. Kristein King
ABC Laboratories
kingk@abclabs.com

Dr. Stephen Klaine
Clemson University
sklaine@clemson.edu

Dr. Joanna Klapacz
Dow Chemical
jklapacz@dow.com

Dr. Joel Kronenberg
Monsanto
joel.m.kronenberg@monsanto.com

Dr. Prem Kumar
Alabama Department of Environmental Management
kpkumar@adem.state.al.us

Dr. Susan Laessig
USEPA
laessig.susan@epa.gov

Ms. Sue Leary
Alternatives Research & Development Foundation
sleary@ardf-online.org

Dr. Ji-Eun Lee
Kellogg Company
ji-eun.lee@kellogg.com

Dr. Craig Llewellyn
The Cocoa-Cola Company
cllewellyn@coca-cola.com

Dr. Emilia Lonardo
Grocery Manufacturers Association
elonardo@gmaonline.org

Ms. Barbara Losey
Alkylphenols & Ethoxylates Research Council
blosey@regnet.com

Dr. Scott Lynn
US EPA
lynn.scott@epa.gov

Dr. Meire Martinez
Faculdade De Medicina De Botucatu
meirebauru@msn.com

Dr. Elizabeth Maull
NTP
maull@niehs.nih.gov

Dr. Niamh McMahon
Dow AgroSciences
nmcmahon@dow.com

Dr. Nora Nock
CWRU
Nora.nock@case.edu

Dr. Gladys Ouedraogo
L'Oréal
gouedraogo@rd.loreal.com

Dr. Sari Paikoff
Defense Threat Reduction Agency
sari.paikoff@dtra.mil

Dr. Grace Patlewicz
DuPont
grace.y.tier@dupont.com

Dr. Geoff Patton
U.S. FDA/CFSAN
geoffrey.patton@fda.hhs.gov

Dr. Nancy Rachman
NJ Rachman Consulting, LLC
njrachman@gmail.com

Dr. Shaila Rao
Chemtura Corporation
shaila.rao@chemtura.com

Mrs. Louette Rausch
Akzo Nobel
louette.rausch@akzonobel.com

Ms. Heather Reddick
Texas Commission on Environmental Quality
Heather.Reddick@tceq.texas.gov

Dr. Linda Roberts
Chevron Energy Technology Company
LRoberts@chevron.com

Dr. Denise Roesh
Chevron
dviq@chevron.com

Dr. Eric Rosenblum
Rosenblum Environmental
ericrosenblum@hotmail.com

Dr. Daniella Ross
Colgate-Palmolive
daniella_urbach-ross@colpal.com

Dr. Larissa Sano
University of Michigan
llubomud@umich.edu

Dr. Shawn Seidel
Dow Corning Corporation
s.seidel@dowcorning.com

Ms. Rachel Shaffer
Environmental Defense Fund
rshaffer@edf.org

Dr. Jie Shen
NCTR/FDA
jie.shen@fda.hhs.gov

Dr. Pramila Singh
Syngenta
pramila.singh@syngenta.com

Dr. Amanda Smolarek
FMC Corporation
amanda.smolarek@fmc.com

Ms. Marize Solano
São Paulo State University
marizesolano@fmb.unesp.br

Dr. Laura Solem
Minnesota Pollution Control Agency
laura.solem@state.mn.us

Dr. Charles Staples
Assessment Technologies, Inc.
cstaples.ati@earthlink.net

Ms. Kristie Sullivan
PCRM
ksullivan@pcrm.org

Dr. David Szabo
US FDA
davidtszabo@gmail.com

Ms. Emily Tipaldo
American Chemistry Council
emily_tipaldo@americanchemistry.com

Dr. Asheesh Tiwary
Chevron
asheesh.tiwary@chevron.com

Mr. Anthony C. Tweedale
R.I.S.K. Consultancy
ttweed@base.be

Dr. Lorraine Twerdok
Twerdok Consulting, LLC
letwerdok@verizon.net

Dr. Luis Valerio
FDA
luis.valerio@fda.hhs.gov

Dr. Katherine von Stackelberg
Harvard Center for Risk Analysis
kvon@hsph.harvard.edu

Dr. William Waissmann
Fiocruz
william.waissmann@gmail.com

Dr. Teresa Wegesser
Chevron
wegt@chevron.com

Dr. Al Wiedow
Linmark Consulting
al.wiedow@linmarkconsulting.com

Dr. Patty Wong
OEHHA/CalEPA
patty.wong@oehha.ca.gov

Ms. Cindy Woodland
Health Canada
cindy.woodland@hc-sc.gc.ca

Dr. Tingting Xu
University of Tennessee
txu2@utk.edu

Ms. Xinyu Yang
Duke University
xinyu.yang@duke.edu

Mr. Buddy Yantz
Lakeside Foods
budman@usfamily.net

Dr. Holly Zahner
U.S. Food and Drug Administration
holly.zahner@fda.hhs.gov

Driving directions to the Workshop from the Homewood Suites Hotel

Trip Duration: 3.7 Miles, 7 minutes

4603 Central Park Dr
Durham, NC 27703

1. Head **west** on **Central Park Dr** toward **S Miami Blvd**

282 ft

2. Turn right onto **S Miami Blvd**

1.1 mi

3. Turn left onto **Cornwallis Rd**

1.2 mi

4. Slight left onto **E Cornwallis Rd**

0.8 mi

5. Turn right onto **T W Alexander Drive**
Destination will be on the right

0.6 mi

15 T W Alexander Dr

Driving directions to the Workshop from the Homewood Suites Hotel

Double Tree Suites by Hilton Raleigh-D
2515 Meridian Pkwy
Durham, NC 27713

1. Head **east** on **Meridian Pkwy** toward **N Carolina 55 W**

0.2 mi

2. Turn left onto **N Carolina 55 W**

1.6 mi

3. Sharp right onto **E Cornwallis Rd**

1.2 mi

4. Turn left onto **T W Alexander Drive**
Destination will be on the right

0.6 mi

15 T W Alexander Dr
Durham, NC 27703

SPONSORS

- Alkylphenols & Ethoxylates Research Council
- American Petroleum Institute
- AMVAC Chemical Corporation
- BASF Corporation
- Battelle
- Center for Alternatives to
- Animal Testing (CAAT/Johns Hopkins)
- Cheminova Consumer Specialty Products Association
- CropLife America Doerenkamp-Zbinden Foundation
- DuPont
- Endocrine Policy Forum
- ExxonMobil Biomedical Sciences, Inc.
- Gowan
- Human Toxicology Project Consortium
- The Humane Society of the United States
- MTBE Consortium
- Personal Care Products Council
- Society of Chemical Manufacturers and Affiliates, Inc.
- Styrene Information and Research Council
- SOT Regulatory Safety Evaluation Specialty Section (RSESS)
- SOT Ethical, Legal and Social Issue Specialty Group (ELSI)
- Syngenta