Dear Colleagues:

I invite you to share your expertise, foster new collaborations, and discover the latest advances in toxicology by attending the SOT 58th Annual Meeting and ToxExpo, March 10–14, 2019, at the Baltimore Convention Center in Baltimore, Maryland.

Featuring more than 100 Featured and Scientific Sessions and 2,100 individual presentations, the SOT Annual Meeting covers basic and cutting-edge science in dozens of toxicological subdisciplines and provides a wealth of information for all career levels, from students to advanced-career toxicologists. Returning for the 2019 meeting are the all-day Poster Sessions introduced last year, and per attendees’ suggestion, SOT will pilot 90-minute Symposium and Workshop Sessions on Tuesday afternoon as part of this year’s scientific program.

More than 6,000 scientists from 50 countries are expected to join SOT in Baltimore. Beyond the scientific program sessions, attendees will enjoy hundreds of additional events, including activities hosted by SOT Regional Chapters, Special Interest Groups, and Specialty Sections; Exhibitor-Hosted Sessions; and other ancillary meetings.

SOT also is pleased to welcome the more than 315 exhibitors who will participate in the three-day ToxExpo. Attendees are encouraged to visit these exhibitors to gain assistance with toxicological products and services, explore expert consulting and collaborative opportunities, and engage in career advancement.

I look forward to welcoming you to Baltimore and joining you in experiencing the best in toxicological research during the largest toxicology meeting in the world.

Sincerely,

Leigh Ann Burns Naas, PhD, DABT, ATS, ERT
2018–2019 SOT President
58TH ANNUAL MEETING & ToxExpo
MARCH 10–14, 2019

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Find up-to-date information at www.toxicology.org/2019 | #2019SOT #toxexpo
Dear Colleagues,

On behalf of the Scientific Program Committee (SPC), the SOT Council, and the rest of the organizing committees for the SOT 58th Annual Meeting and ToxExpo, I am pleased to announce the scientific program for the 2019 event.

As always, the SPC goal was to construct a program which presents both the best science and the breadth of SOT member interests. We believe that the 2019 Symposia, Roundtables, Workshops, and other Scientific and Featured Sessions fulfill this goal, as they are timely and highly informative and span a full spectrum of topics to reflect the diversity of the SOT membership. In addition, this year there are six sessions with the designation Innovations in Applied Toxicology (IAT) or Innovations in Toxicological Sciences (ITS).

New in 2019 are 90-minute Symposium and Workshop Sessions, which will take place on Tuesday afternoon.

The 2019 Featured Sessions will highlight cutting-edge and impactful research, presented by leading scientists. The Opening Plenary Lecture will feature a presentation on the robust assembly of human tissues for disease modeling and discovery by William L. Murphy of the University of Wisconsin-Madison. The Plenary Keynote Medical Research Council (MRC) Lecture on Wednesday will be presented by Janet M. Lord of the University of Birmingham Institute of Inflammation and Ageing on a subject that is beginning to receive much attention: ageing and multimorbidity.

SOT partnerships with EUROTOX and the Japanese Society of Toxicology (JSOT) continue this year, with the SOT/EUROTOX debate tackling the proposition “Classification of Substances as Endocrine Disruptors Has a Public Health Benefit” and the SOT/JSOT Symposium focusing on epigenetic modification of chronic pathology and toxicology. Leading SOT, EUROTOX, and JSOT toxicologists will participate in these sessions.

This year’s Award Lectures will include presentations from the winners of the Merit Award, Distinguished Toxicology Scholar Award, and Translational Impact Award. This year’s EUROTX Bo Holmstedt Award Lecture on metabolism, inflammation, and cancer will be presented by Nigel J. Gooderham.

If you have late-breaking research to share, we welcome your abstract submission for inclusion in a Late-Breaking Poster Session. The submission fee for late-breaking abstracts is $75. More information about submitting a late-breaking abstract is available on the SOT Annual Meeting website.

I look forward to seeing you during the more than 90 Scientific Sessions and Continuing Education courses and 2,100 individual presentations at the 2019 SOT Annual Meeting and ToxExpo.

Warmest regards,

Ronald N. Hines, MS, PhD, ATS
SOT Vice President and Scientific Program Committee Chairperson, 2018–2019
### Sunday, March 10

#### 7:00 AM to 7:45 AM

**CONTINUING EDUCATION SUNRISE MINI-COURSES**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>SR01</td>
<td>Handling Uncertainties in Evaluating Mixtures: What’s the Difference between a “Similar” and a “Sufficiently Similar” Mixture?</td>
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<tr>
<td>SR02</td>
<td>Publicly Available Exposure Tools to Inform the Toxic Substances Control Act</td>
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#### 8:15 AM to 12:00 Noon

**CONTINUING EDUCATION MORNING COURSES**

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<tbody>
<tr>
<td>AM03</td>
<td>Assay Development Principles and Good Research Practices for Rigor and Reproducibility in <em>In Vitro</em> Toxicology</td>
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<tr>
<td>AM04</td>
<td>Complex Mixtures and UVCBs: Analysis, Testing, and Risk Assessment</td>
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<tr>
<td>AM05</td>
<td>Developmental Toxicity of the Skeletal System: Interpretation of Findings in DART Studies and Implications for Risk Assessment</td>
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<tr>
<td>AM06</td>
<td>Industrial Application of Computational Toxicology in the 21st Century</td>
</tr>
<tr>
<td>AM07</td>
<td>Role of Toxicokinetics in Human Health Safety Assessments</td>
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<tr>
<td>AM08</td>
<td>Mechanistic Understanding and Quantitative Risk Assessment in Immunotoxicology</td>
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#### 1:15 PM to 5:00 PM

**CONTINUING EDUCATION AFTERNOON COURSES**

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<th>#</th>
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<tbody>
<tr>
<td>PM09</td>
<td>Applications and Review of Physiologically Based Pharmacokinetic Modeling for Regulatory Risk Assessment</td>
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<tr>
<td>PM10</td>
<td>Beauty of the Skin Is in the Eye of the Beholder: A Basic Course on Dermal and Ocular Toxicology</td>
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<tr>
<td>PM11</td>
<td>Conducting Systematic Review in Toxicology—Why, When, How?</td>
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<tr>
<td>PM12</td>
<td>Current Dose-Response Modeling Strategies and Applications in Chemical Risk Assessment</td>
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<tr>
<td>PM13</td>
<td>Microbiome and Environmental Toxicants: From Study Design and Analysis to Regulatory Guidance</td>
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<tr>
<td>PM14</td>
<td>Structural and Functional Alterations of Mitochondria in Chemically Induced Cytotoxicity</td>
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</tbody>
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### Monday, March 11

#### 8:00 AM to 9:00 AM

**PLENARY SESSION**

**Robust Assembly of Human Tissues for Disease Modeling and Discovery**

*Lecturer: William L. Murphy, University of Wisconsin-Madison, Madison, WI.*

“Dr. Murphy will enlighten us on his interdisciplinary approaches to develop innovative biomaterials, or as he describes, ‘bioinspired materials,’ because they mimic the fascinating ways that nature builds materials—including human organs. Such materials are quickly being adopted by toxicologists to bridge the gap between alternative methods that rely on molecular- and cellular-based platforms and whole organs or organisms. His lecture promises to be of particular interest to anyone interested in the development of new alternative methods and how these methods can be used to fulfill the vision of toxicity testing in the 21st century.”

~ Ron Hines, Chair, Scientific Program Committee
### 9:15 AM to 12:00 Noon

**SYMPOSIUM SESSIONS**
- Advances in *In Vitro* to *In Vivo* Extrapolation: Approaches and Applications
- Alpha-Synuclein: A Good Protein Turned Bad in Chronic Brain Diseases with Toxicological Implications
- Assessing Acute Health Risk: Potential Application of Next-Generation Toxicological Tools
- Novel Genetic-Based Tools for Evaluating Toxicity Potential, Mechanism of Action, and Population Dynamics

**WORKSHOP SESSIONS**
- Application of Computational Modeling to Risk Assessment of Endocrine Disruptors
- MALDI Tissue Imaging: A New Tool for Making TK/TD Connections to Histopathology
- Mechanisms and Effects of Diabetogenic Environmental Metals: Type II Diabetes Mellitus and Diabetic Kidney Disease
- Pharmaceutical Investigative Toxicology: Case Studies in Optimizing Drug Discovery and Guiding Human Risk Assessment

**PLATFORM SESSIONS**
- Investigating Mode of Action in Chemical Carcinogenesis
- SPC Highlights Emerging Scientists: Mechanistic Toxicology to Decode Injury and Repair

### 9:15 AM to 4:30 PM

**POSTER SESSIONS**
- Air Pollution Toxicology
- Air Pollution: Biomass
- Air Pollution: Ozone
- Air Pollution: PM
- Animal Models
- Biomarkers of Disease and Exposure
- Clinical and Translational Toxicology
- Ecotoxicology
- Genetic Toxicity
- Liver I
- Liver II
- Neurodegenerative Disease
- Neurodegenerative Disease: Parkinson's Disease
- Neurotoxicity: Developmental
- Neurotoxicity: General
- Neurotoxicity: Metals
- Neurotoxicity: Pesticides
- Perfluorinated Alkyl Substances
- Persistent Organic Pollutants
- Reproductive Toxicology I
- Reproductive Toxicology II
- Safety Assessment Pharmaceutical: Drug Discovery
- Stem Cell Biology and Toxicology

### 9:30 AM to 3:00 PM

**RESEARCH FUNDING INSIGHTS**
- Network with Program Officers

### 12:10 PM to 1:30 PM

**ROUNDTABLE SESSION**
- Data for Chemical Evaluations: Secret or Otherwise

### INFORMATIONAL SESSIONS
- Electronic Waste: An Evolving Global Health Concern and Risk Assessment Challenge
- Federal Efforts in Rapidly Assessing Hazard and Risk to Emerging Threats and Emergency Response

### 12:30 PM to 1:30 PM

**DISTINGUISHED TOXICOLOGY SCHOLAR AWARD LECTURE**
- To be announced
### SYMPOSIUM SESSIONS

- Immune-Epithelial Cell Crosstalk in Lung Toxicology and Disease
- Patterns of Co-exposure and Its Implications for Understanding the Health Effects of Mixtures
- Scaling Barriers: Cellular Dynamics and Models of Blood-Brain Barrier Developmental Toxicity
- Strategic Development of Read-Across within the EU-ToxRisk Project and Beyond

### WORKSHOP SESSIONS

- A Herculean Switch? Rethinking Chemical Carcinogenicity Assessment
- A Tale of an *In Vitro* Method: From Inception to International and Regulatory Acceptance
- Applying Systems Biology Approaches to Understand the Joint Action of Chemical and Nonchemical Stressors
- NextGen Renal Proximal Tubule Toxicity Screening: Novel Cellular Model and Complex Culture Platforms

### PLATFORM SESSIONS

- Oxidant-Mediated Injury in Toxicology
- Safety Assessment: Pharmaceutical—Drug Discovery

### 4:30 PM to 5:50 PM

### EDUCATION-CAREER DEVELOPMENT SESSION

- Models and Strategies for Building Diversity and Inclusion in Toxicology

### 4:45 PM to 6:00 PM

### SOT/EUROTOX DEBATE

**Classification of Substances as Endocrine Disruptors Has a Public Health Benefit**

*Debaters: Paul Foster, NIEHS (Retired), Research Triangle Park, NC; and Martin van den Berg, Utrecht University, Utrecht, Netherlands.*

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**Tuesday, March 12**

### 8:00 AM to 10:45 AM

### SOCIETY OF TOXICOLOGY AND JAPANESE SOCIETY OF TOXICOLOGY SYMPOSIUM

**Epigenetic Modification of Chronic Pathology and Toxicology**

*Lecturers: Masatoshi Hagiwara, Kyoto University, Kyoto, Japan; Jun Kanno, Japan Bioassay Research Center, Kanagawa, Japan; Dana C. Dolinoy, University of Michigan School of Public Health, Ann Arbor, MI; and Cheryl Lyn Walker, Baylor College of Medicine, Center for Precision Environmental Health, Houston, TX.*
8:00 AM to 10:45 AM (Tuesday continued)

**SYMPOSIUM SESSIONS**

- “Not Your Father’s ED”: Expanding the Definition and Understanding of Endothelial Dysfunction (ED) Due to Inhaled Toxicants
- Stem Cells and Metals Toxicity: From Tissue Regeneration and Repair to Carcinogenesis
- Systems Toxicology Approaches to the Science of Safety Evaluation
- Using Zebrafish as a Model to Understand and Ultimately Prevent Neurotoxicity

**WORKSHOP SESSIONS**

- Emergent Mechanisms of Cytochrome P450 Gene Regulation: Defining an Improved Roadmap toward 21st-Century Pharmacogenomics
- Predicting Metabolic Clearance Rates for Drug Leads and Environmental Chemical Risk Assessment
- Shifting Currents in Predictive Toxicology and Safety Evaluation with In Vitro and Alternative Approaches
- Strategies to Mitigate the Health Impacts of Air Pollutants in Susceptible Populations

**PLATFORM SESSION**

- SPC Highlights Emerging Scientists: Adverse Effects of Perfluorinated Alkyl Substances

9:15 AM to 4:30 PM

**POSTER SESSIONS**

- Alternatives to Mammalian Models I
- Alternatives to Mammalian Models II
- Autoimmunity and Hypersensitivity
- Bioinformatics
- Biological Modeling
- Carcinogenesis I
- Carcinogenesis II
- Cardiovascular Toxicology/Hemodynamics
- Cell Death and Apoptosis
- Chemical Threats and Bioterrorism I
- Chemical Threats and Bioterrorism II
- Computational Toxicology I
- Computational Toxicology II
- Developmental and Juvenile Toxicology
- Developmental Basis of Adult Disease
- Education, Ethical, Legal, and Social Issues
- Exposure Assessment and Biomonitoring
- Immunotoxicity
- Metals I
- Metals II
- Nanotoxicology In Vitro: Alternative Testing Strategies
- Nanotoxicology In Vitro: Mechanism, Uptake, and Cellular Response
- Nanotoxicology: In Vivo
- Oxidative Injury and Redox Biology
- Pesticides
- Respiratory Toxicology
- Risk Assessment I
- Safety Assessment Pharmaceutical: Drug Development
- Systems Toxicology and Biology
- Tobacco and Electronic Nicotine Delivery Systems

9:30 AM to 4:30 PM

**RESEARCH FUNDING INSIGHTS**

- Network with Program Officers

11:00 AM to 12:00 Noon

**MEET THE DIRECTORS**

**A Conversation with Linda S. Birnbaum, Jennifer Orme-Zavaleta, and Mark S. Johnson**

### 11:00 AM to 12:00 Noon

<table>
<thead>
<tr>
<th><strong>TRANSLATIONAL IMPACT AWARD LECTURE</strong></th>
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### 11:00 AM to 12:20 PM

<table>
<thead>
<tr>
<th><strong>ROUNDTABLE SESSION</strong></th>
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<tbody>
<tr>
<td>The Delaney Clause, from 1958 to 2019: Making the Model Relevant</td>
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</table>

### INFORMATIONAL SESSIONS

- Challenges and Opportunities Encountered with TSCA Reform: Working toward a Shared Vision for Product Safety
- Science at the Nexus of Wildfire Smoke and Public Health

### 12:30 PM to 1:30 PM

<table>
<thead>
<tr>
<th><strong>MERIT AWARD LECTURE</strong></th>
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### 1:00 PM to 2:30 PM

<table>
<thead>
<tr>
<th><strong>TOXICOLOGICAL SCIENCES FEATURED SESSION</strong></th>
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<tbody>
<tr>
<td>From the Pages of ToxSci: Mouse vs. Machine … Are Animal Studies Being Supplanted by Computers?</td>
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<tr>
<td>Panelists: Gary W. Miller, Columbia University, New York, NY; Alison Harrill, NIEHS/NTP; Research Triangle Park, NC; Thomas Hartung, Johns Hopkins University Center for Alternatives to Animal Testing (CAAT), Baltimore, MD; Nicole C. Kleinstreuer, NIEHS, Research Triangle Park, NC; and Ivan Rusyn, Texas A&amp;M University, College Station, TX.</td>
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### 1:00 PM to 2:30 PM

<table>
<thead>
<tr>
<th><strong>SYMPOSIUM SESSIONS</strong></th>
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<tbody>
<tr>
<td>Explicating the Pathogenic Environmental Factors in Nonalcoholic Fatty Liver Disease</td>
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<td>Integrated ‘Omics Approaches to Toxicity Assessments</td>
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<tr>
<td>Scientific and Regulatory Update in the Application of the 3Rs Principle in Chemical and Drug Development</td>
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### WORKSHOP SESSIONS

- Adverse or Not-Adverse? Thinking Process behind Adversity Determination during Nonclinical Drug Development
- Assessing the Bisphenol Class of Chemicals
- *In Vitro* Static and Dynamic Skin Metabolism Methods and Strategies to Address the Safety Assessment of Topically Applied Chemicals
- Innovation in Biomarker Qualification

### 2:30 PM to 3:00 PM

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<th><strong>NETWORKING TIME</strong></th>
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**Wednesday, March 13**

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<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:00 AM to</td>
<td>SYMPOSIUM SESSIONS</td>
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<tr>
<td>10:45 AM</td>
<td>• Establishing Effective Alternatives for Acute Oral and Inhalation Systemic Toxicity Testing</td>
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<td>• Progress toward Charting the Course for Improving Carcinogenicity Assessments of Human Pharmaceuticals and Pesticides</td>
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<td>• The Role of Dynamic RNA Modifications in Environmental Response and Disease</td>
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<td>WORKSHOP SESSIONS</td>
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<td></td>
<td>• A Sharp Stick in the Eye: Understanding and Managing Ocular Findings in General Toxicology Studies</td>
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<td>• Can We Panelize Seizure?</td>
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<td>• Nerve Agent Poisoning: Mechanisms of Toxicity, Recent Releases, Verification, and Innovative Treatment Approaches</td>
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<td>• Pregnant and Vaping: Knowns and Unknowns of Reproductive and Developmental Toxicity Related to Electronic Cigarettes</td>
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<td>• Understanding the Impact on the Immune System of Occupationally Relevant Exposures to Multiwalled Carbon Nanotubes</td>
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<td>PLATFORM SESSIONS</td>
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<td>• Safety Assessment: Pharmaceutical—Drug Development I</td>
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<td>• SPC Highlights Emerging Scientists: Biopharmaceutical Safety Assessment</td>
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<td>• Xenobiotic Disposition in Disease and Toxicities</td>
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</tbody>
</table>
**9:15 AM to 4:30 PM (Wednesday continued)**

**POSTER SESSIONS**

- Alternatives to Mammalian Models III
- Biotransformation and Cytochrome P450 Metabolism
- Disposition and Pharmacokinetics
- Emerging Technologies
- Endocrine Toxicology
- Epidemiology and Human Population Studies
- Epigenetics
- Food Safety and Nutrition
- Gene Regulation
- Inflammation
- Mechanisms of Kidney Toxicity
- Medical Devices
- Mixtures
- Natural Products
- Ocular Toxicity
- Receptors
- Regulatory Policy and Methods
- Risk Assessment II
- Safety Assessment: Nonpharmaceutical
- Skin

**9:30 AM to 4:30 PM**

**RESEARCH FUNDING INSIGHTS**

- Network with Program Officers

**11:00 AM to 12:00 Noon**

**EUROTOX BO HOLMSTEDT MEMORIAL AWARD LECTURE**

**Metabolism, Inflammation, and Cancer**

*Lecturer: Nigel J. Gooderham, Imperial College London, London, United Kingdom.*

“Professor Gooderham was selected as the Bo Holmstedt Memorial Lecturer from a strong field of European toxicologists. With interests in mechanisms of chemical carcinogenesis and molecular and cellular responses to toxicity, his presentation describes the role of microRNAs in colon carcinogenesis.”

~ Heather Wallace, EUROTOX President 2018–2020

**11:00 AM to 12:20 PM**

**ROUNDTABLE SESSION**

- The Necessity of Uncertainty: Quantifying Uncertainty for Regulatory Application of New Approach Methodologies

**INFORMATIONAL SESSION**

- Toxicology Education and Risk Assessment Training in Africa: Status, Challenges, and Role of SOT Special Interest Groups in Moving Forward

**EDUCATION–CAREER DEVELOPMENT SESSION**

- Stepping Out of the Lab: Maximizing Access and Experience for Internships in Toxicology
PLENARY KEYNOTE MEDICAL RESEARCH COUNCIL (MRC) LECTURE

Ageing and Multimorbidity: Time for a New Approach

**Lecturer:** Janet M. Lord, University of Birmingham Institute of Inflammation and Ageing, Birmingham, United Kingdom.

“Professor Janet Lord will tell us about the many factors that make aging unpleasant, and a few that are important in lessening the impact of age. This talk will be especially important to those of us who are interested in the interplay of factors that contribute to chronic diseases with environmental etiologies.”

~ George P. Daston, Co-Chair, Scientific Program Committee

1:30 PM to 4:15 PM

SYMPOSIUM SESSIONS

- Consideration for Safety Assessment of Chemically Synthesized Therapeutic Peptides: A Drug Development Paradigm between the Large and Small
- Role of Oxidative Stress in Health and Disease: Mechanisms, Methods of Detection, and Biomarkers
- Understanding the Utility of *In Vitro* Developmental Toxicity Assays and Building Integrated Testing Strategies

WORKSHOP SESSIONS

- Air Pollution-Induced Cardiovascular Toxicity: Endothelial Progenitor Cells as Critical Mediators
- Microphysiological Systems: A New Era in Neurotoxicology?
- Order from Chaos: Pattern Recognition in Challenging Human Health Datasets
- Risk Assessment of Consumer Products and Articles: Critical Considerations and Case Studies for Characterizing and Quantifying Consumer-Relevant Exposures to Chemicals and Nanomaterials
- This Is Your Teen Brain on Drugs: In Search of Biomarkers Unique to Dependence Toxicity in Adolescents [1AT]

PLATFORM SESSION

- Immunotoxicity

4:30 PM to 5:30 PM

LEADING EDGE IN BASIC SCIENCE AWARD LECTURE

- To be announced

4:30 PM to 5:50 PM

ROUNDTABLE SESSION

- A Multi-Stakeholder Dialogue on Using Proprietary Modeling Platforms to Support Risk Assessment and Regulatory Decisions

EDUCATION-CAREER DEVELOPMENT SESSION

- Navigating Turbulent Waters: How to Address Conflict throughout Your Career
<table>
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<tr>
<th>8:30 AM to 11:15 AM</th>
<th>SYMPOSIUM SESSIONS</th>
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<tr>
<td></td>
<td>Nerve Agent and Pesticide Poisoning: Best Practice Methodologies for Assessing Long-Term Health Effects</td>
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<td>New Mechanistic Insights into Causes and Outcomes of Epigenetic Dysregulation by Carcinogenic Metals</td>
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<td>Preconception Exposure to Toxicants: Assessing Gamete Quality and Reproductive Outcomes</td>
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<tr>
<td>Potential Alternatives to Systematic Review: Evidence Maps and Scoping Reviews</td>
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<tr>
<td>Use of Adverse Outcome Pathways to Design Nonanimal Testing Strategies for Assessing Inhalation Toxicity</td>
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<td>Cardiovascular Toxicology/Hemodynamics</td>
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<td>Nanotoxicology: In Vitro Test Platform</td>
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<tr>
<td>Safety Assessment: Pharmaceutical—Drug Development II</td>
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<td>Safety Assessment: Pharmaceutical—Drug Discovery II</td>
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<th>8:30 AM to 11:30 AM</th>
<th>LATE-BREAKING POSTER SESSION</th>
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**SOT Going Digital in 2019**

New in 2019, all meeting materials available exclusively online.

Mobile Event App available for download in February 2019 from all the major app stores.


Program PDF | January 2019
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The Toxicologist PDF | February 2019
SOT Mobile Event App | February 2019

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Find up-to-date information at [www.toxicology.org/2019](http://www.toxicology.org/2019) | #2019SOT #toxexpo
The Society of Toxicology (SOT) has established a special category for private, public, and not-for-profit organizations that wish to contribute to the success of the Society through year-round support. You, too, can become among those organizations that demonstrate their commitment to the SOT mission of “creating a safer and healthier world by advancing the science and increasing the impact of toxicology.” Organizations interested in becoming an SOT Global Partner should contact SOT Headquarters.

Here’s Why You Should Support SOT

By becoming an SOT Global Partner, organizations are:

- Supporting the premiere toxicology society in increasing the scientific impact of and advocating for the value of toxicology;
- Contributing to the success of the largest scientific meeting in toxicology and attracting scientists at all stages of their careers from around the globe;
- Promoting the importance of education and building for the future of toxicology; and
- Encouraging activities aligned with the prediction and prevention of toxicity and disease.

AbbVie, Inc.
North Chicago, Illinois

AstraZeneca
Cambridge, United Kingdom

Bristol-Myers Squibb Company
Pennington, New Jersey

Celgene Corporation
Summit, New Jersey

Chevron Energy Technology Company
Houston, Texas

The Coca-Cola Company
Atlanta, Georgia

The Colgate-Palmolive Company
Piscataway, New Jersey

Covance Inc.
Madison, Wisconsin

The Dow Chemical Company
Midland, Michigan

DuPont Haskell Global Center for Health Sciences
Newark, Delaware

Envigo CRS Ltd.
Huntingdon Cambridgeshire, United Kingdom

ExxonMobil Biomedical Sciences, Inc.
Annandale, New Jersey

Genentech, Inc.
South San Francisco, California

Gilead Sciences, Inc.
Foster City, California

Novartis
East Hanover, New Jersey

Oxford University Press
Oxford, United Kingdom

Pfizer, Inc.
Groton, Connecticut

Procter & Gamble Company
Mason, Ohio

Regeneron Pharmaceuticals, Inc.
Tarrytown, New York

Sanofi
Bridgewater, New Jersey

Syngenta Crop Protection, Inc.
Greensboro, North Carolina

Takeda Pharmaceutical Company Limited
Cambridge, Massachusetts
Attend the Meeting

Reasons to Attend

**Innovative Science**
From the Plenary Lecture by William L. Murphy, University of Wisconsin-Madison, on the use of alternative methods and organs-on-a-chip for both basic mechanistic studies and toxicology testing to the more than 80 Featured and Scientific Sessions, the SOT Annual Meeting features the latest advancements and cutting-edge research in toxicology, as well as updates related to basic science research.

**Professional Development and Education**
The meeting’s 14 Continuing Education courses cover a range of topics, from established knowledge in toxicology to new developments. In addition, there are four Education-Career Development Sessions in the Scientific Program and exclusive events designed to support the development of postdoctoral scholars and graduate students by furthering their toxicology understanding and careers.

**Global Networking and Partnerships**
The three-day ToxExpo features more than 315 exhibitors, providing an array of services and products, subject-matter expertise, and career opportunities for toxicologists. More than 100 social events, hosted by SOT-affiliated groups and partners, provide additional opportunities for connecting with fellow attendees from more than 50 countries.

**Affordability and Value**
Discounted registration fees are available for SOT members, postdoctoral scholars, graduate students, and attendees from developing countries. In addition, SOT has added one-day registration passes for 2019 to increase access to the groundbreaking science and presentations. SOT also arranges exclusive hotel rates and travel discounts associated with the meeting.
Planning to Attend

Accessibility for Persons with Disabilities

The Baltimore Convention Center and most of the SOT hotels are accessible to persons with disabilities. If you require special services, please let SOT know by indicating your needs while registering or by contacting Heidi Prange by email at heidi@toxicology.org or by phone at 703.438.3115.

To arrange special services, SOT recommends the following two providers for language and mobility needs.

Language Services Associates, Inc.

800.305.9673 | www.lsaweb.com

Language Services Associates (LSA) is a nationwide, full-service firm providing translators and interpreters in 180 languages.

Scootaround

888.441.7575 | www.scootaround.com

Scootaround is a leading source for wheelchair, scooter, and powerchair rentals.

Attire

Business casual. No coat or tie required! Bring comfortable clothing and shoes for walking the large conference center. Dress in layers, as meeting rooms sometimes fluctuate in temperature.

Badges and Event Tickets

If you register by January 11, 2019, you will receive your badge and event tickets in the mail. Please remember to bring these items with you to Baltimore, as your badge admits you to the meeting, sessions, and events. Tickets for Continuing Education courses and other events also may be required and are issued with your meeting badge.

If you register after January 11, 2019—or do not receive your badge or misplace it—go to a Registration counter on-site to pick up your badge. You will be asked to show a photo ID. Badge holders will be available on-site near Registration.

Visa Information

Tips for Applying for a Visa

- **Start Early**—The United States is advising visa applicants to apply at least three to four months before their travel date. Also, additional reviews may be required. This could add four to six weeks to the processing time.
- **Gathering Your Application Materials**—Organize your passport; necessary applications; supporting documents, including information on employment, reason for travel, and financial status; and proof of payment of fees. For more detailed information on visa requirements, consult the US Department of State’s visa site and the International Visitors Office of the National Academies.
- **Submitting Your Application**—Make an appointment to visit your US Embassy or Consulate. Make sure you ask if there are any fees required. Most fees must be paid before your appointment. Wait times for appointments may be longer than in the past. Schedule the appointment as soon as possible. Information on visa wait times can be found on the US Department of State website.

If you need additional visa assistance, contact the [International Visitors Office of the National Academies](https://www.nationalacademies.org/visitors).

If you need a formal invitation letter for visa purposes, you may request an invitation by sending your name, address, and other contact information to the SOT Registration Department by email at sotmeetings@toxicology.org or calling 703.438.3115. If you have been accepted to make a presentation at the meeting, please include the name and date of your presentation. You will need to make your own hotel reservations and register for the meeting.
Safety and Security

Personal Safety
The best way to stay safe is to be aware of your surroundings and to avoid situations where you feel uncomfortable.

Walk “smart” when you leave the Baltimore Convention Center:
» Take off your badge when you leave the convention center.
» Establish a “buddy” system with another meeting attendee and don’t walk alone. Also, share schedules and check on each other periodically.
» Know your destination and the best way to reach it. Avoid shortcuts that take you into unoccupied, unlighted areas or isolated streets.
» Keep your cell phone charged and never let strangers borrow it.
» Carry bags, purses, and valuables in front of your body. Jackets with pockets provide a convenient alternative to reduce the chance for lost or stolen handbags. Laptop computers are attractive, easy targets for thieves, so be sure your laptop is in a secure place.

If you see something, say something! Report suspicious activity to authorities.

In Case of Protests
The possibility of demonstrators is very real given the nature of the SOT meeting. Events of this nature range from verbal confrontations, protests, and strikes to riots. The following procedures are recommended in the event of demonstrations:
» To identify yourself as an official meeting attendee, always wear your name badge while in the Baltimore Convention Center. When leaving the facility, remove your badge to appear to be a resident of the city. Avoid being distracted by your mobile phone.
» If you see a demonstration or protest beginning, please contact any member of the SOT Annual Meeting staff, and they will initiate an SOT response. If you see actions that appear threatening, notify the nearest security officer.
» Do not engage, defend either side, or subdue anyone in any type of disturbance. Demonstrators are usually trying to attract media attention. Don’t help them!
» SOT representatives will respond to media inquires. Do not participate in interviews or other media responses.
» In the unlikely event that outsiders disrupt a Scientific Session or other event, SOT security officials have well-developed contingency plans in place. Please follow directions from the chairperson and avoid becoming involved in the situation.

Baltimore Hospitality Guides
Baltimore has Hospitality Guides available to escort you while walking to your hotel or waiting for a taxi after dark:
» Guides are available every day from 10:30 am–9:00 pm for areas north and east of the Inner Harbor. Anyone wishing to receive an escort should call 410.802.9631.
» Additional guides are available along the waterfront from 9:30 am–10:00 pm (Sunday–Thursday) and 9:30 am–11:00 pm (Friday–Saturday) by calling 443.278.4701. They will meet you at your location and walk with you to your Inner Harbor/Harbor East destination.
Hotel and Travel

Housing
The Society of Toxicology has reserved and arranged for discounted room rates at various Baltimore hotels—known as the SOT hotel room block. Booking a room in the room block is an important way to support the Society and keep overall meeting costs as low as possible. By booking a room in the SOT hotel room block through the SOT official housing partner, Connections Housing, you get exclusive hotel rates, increase your networking opportunities by staying in the same locations as other attendees and exhibitors, and receive full-service assistance in finding and securing the perfect room and making updates to your reservation without any prepayment.

Hotel Reservation Information
All housing reservations must be made through Connections Housing and not directly with the hotels. The deadline for housing reservations is February 7, 2019. Please choose only one of the methods below to make your reservation. For best availability and immediate confirmation, make your hotel reservation via internet or by telephone. Faxed and mailed housing requests will take longer to process, and your hotel selections may not be available.

Book Online:
www.toxicology.org/housing

Mail:
Connections Housing
950 Scales Road, Building 200
Suwanee, GA 30024 United States

Tel:
800.262.9974 (US) or 404.842.0000
(U.S. and outside the U.S.)

Fax:
678.228.1920
(U.S. and outside the U.S.)

Hours of Operation:
8:30 AM–7:00 PM (EST)
Monday–Friday

Hotel Acknowledgment
A reservation acknowledgment will be emailed, faxed, or mailed to you via Connections Housing once your reservation has been booked. (You will not receive a confirmation from your hotel.) If you do not receive an acknowledgment within three business days, please call Connections Housing.

Changes and Cancellations
You can make changes and/or cancellations online or by contacting Connections Housing at 404.842.0000 or 800.262.9974. The hotel will charge the first night’s room and tax to individuals who cancel their reservations within 72 hours prior to the day of arrival or who do not arrive at all. Early departures are subject to penalty fees set by the hotel.

Room-Share Program
The Society is pleased to provide a Room-Share Program to those registered for the Annual Meeting. It is available to each meeting registrant who voluntarily enrolls in the program and accepts the terms of the legal disclaimer. This program allows SOT Annual Meeting registrants to identify others with whom a room might be shared. For more information on this program and to sign up, visit the SOT Annual Meeting website.
Transportation

Air Transportation
Baltimore is serviced by Baltimore/Washington International Thurgood Marshall Airport (BWI), which is a 20-minute drive from the Baltimore Convention Center and the SOT hotel area. The airport offers 688 flights daily on 36 different carriers.

Preferred Carrier Airfare Discounts
SOT has established discounted rates through United and Delta Airlines on select routes to Baltimore. Be sure to use the appropriate reference numbers when making your reservation. You may purchase your ticket online, call the airline directly using the toll-free number, or provide your travel agent with the reference/discount numbers listed below to receive the discount.

United Airlines
Tel: 800.426.1122
www.united.com
SOT Discount Code: ZFZ7, 253970
Use Z Code ZFZ7 and Agreement Code 253970 to receive a discount of up to 10%. The discount is valid for travel from March 4, 2019, through March 18, 2019.

Attendees coming from outside the US should call their local United Airlines reservations office or email groupmeetings@united.com with their preferred itinerary and discount codes.

If you are booking through a travel professional, please give them the following information to receive a discount:

Delta Airlines
Tel: 800.328.1111
www.delta.com/meetings
SOT Discount Code: NY2HK
Use offer code NY2HK to receive a discount of up to 10%. The discount is valid for travel from March 4, 2019, through March 18, 2019.

Attendees coming from outside the US should call their local Delta Airlines reservations office or email deltameetingnetwork@delt.com with their preferred itinerary and discount codes.

SOT Air Travel Provider—ATC Travel Management
ATC Travel Management is the official travel management firm for the SOT 58th Annual Meeting and ToxExpo.

Tel: 800.458.9383 | Email: reservations@atcmeetings.com
Hours of Operation: Monday–Friday, 8:30 AM–7:00 PM (EST)

Please note that depending on your reservation method, ATC Travel Management charges a $10 online service fee or a live-agent reservation fee.

Before contacting ATC Travel Management, please gather the following information:

• Your name as it appears on your ID and your date of birth
• The desired dates of arrival to and departure from Baltimore
• Your home city or originating airport
• Your approximate time of departure from the originating airport
• The number of persons traveling (adults/children)
• Your payment method, either credit card or check
• Your airline frequent flyer number(s)

To obtain the maximum discounted fares, call at least 60 days prior to departure and identify yourself as a Society of Toxicology meeting attendee. ATC Travel Management will find the best fare for you and email you an itinerary.
**Hotel & Travel**

**Ground Transportation from the Airport**

Ground transportation is located curbside outside the baggage claim area.

**Shuttle Services**

SuperShuttle and Execucar provide the most cost-effective ground transportation service between BWI Airport and major hotels in the downtown area. Shuttle service is operated 8:00 am–12:00 midnight daily.

A discount for each service is available by using the discount code 4K6T8:

- 10% off all SuperShuttle and Execucar private airport sedans and SUVs

This discount is valid for online reservations only. For more details on booking or finding a SuperShuttle at the airport, please see the SOT SuperShuttle Promotional Flyer.

**Car Rental**

Passengers arriving on flights should take the free shuttle from the lower level of the terminal for a 10-minute ride to the rental car facility. The 11 different car rental agencies that service the airport can be found on the BWI website.

**Taxi**

The taxi stand is located just outside the baggage claim area of the lower level of the terminal. Taxis are prohibited from charging flat rates. For more information, call 410.859.1100 or visit www.bwiairporttaxi.com.

**Train Transportation**

**AMTRAK**

Tel: 800.872.7245 | www.amtrak.com

Amtrak operates out of Penn Station, which is a 20-minute drive from the Baltimore Convention Center and the SOT hotel area. There are always taxis ready and waiting outside the station.

**Getting around Town**

**Public Transportation**

The Maryland Transit Administration (MTA) operates bus, Metro Subway, Light Rail, and MARC train services. For fares and schedules, please call 888.218.2267 or 410.539.5000 or visit www.mta.maryland.gov.

The Charm City Circulator is a free transportation service with four routes that intersect downtown Baltimore, including a route to Fort McHenry National Monument and Historical Shrine. The routes also connect to other forms of transit, such as the Light Rail, MARC, Metro Subway, and Baltimore Water Taxi.

**Ride-Share Program**

SOT is offering a Ride-Share Program in conjunction with the Annual Meeting and ToxExpo for those who wish to reduce travel expenses. Once you have registered for the Annual Meeting, you can enroll in the Ride-Share Program, view other enrollees, and make transportation arrangements.

**Baltimore Convention Center Location and Parking**

**Baltimore Convention Center**

1 West Pratt Street, Baltimore, MD 21201

Ample public parking is available in proximity to the convention center for an hourly/daily fee. Check the Baltimore Convention Center website for more information about parking.

Please review the SOT Hotel Accommodations and Services (or the following two pages) for valet parking and self-parking rates for your hotel.

Find up-to-date information at www.toxicology.org/2019 | #2019SOT twitter toxexpo
## Hotel Map

<table>
<thead>
<tr>
<th></th>
<th>Hotel Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baltimore Marriott Inner Harbor at Camden Yards</td>
</tr>
<tr>
<td>2</td>
<td>Baltimore Marriott Waterfront</td>
</tr>
<tr>
<td>3</td>
<td>Days Inn Inner Harbor</td>
</tr>
<tr>
<td>4</td>
<td>Embassy Suites by Hilton Baltimore Inner Harbor</td>
</tr>
<tr>
<td>5</td>
<td>Hampton Inn Baltimore-Downtown/Convention Center</td>
</tr>
<tr>
<td>6</td>
<td>Hilton Baltimore (SOT Headquarters Hotel)</td>
</tr>
<tr>
<td>7</td>
<td>Holiday Inn Inner Harbor-Downtown Baltimore</td>
</tr>
<tr>
<td>8</td>
<td>Hotel Monaco Baltimore, A Kimpton Hotel</td>
</tr>
<tr>
<td>9</td>
<td>Hyatt Regency Baltimore Inner Harbor</td>
</tr>
<tr>
<td>10</td>
<td>Lord Baltimore Hotel</td>
</tr>
<tr>
<td>11</td>
<td>Renaissance Baltimore Harborplace Hotel</td>
</tr>
<tr>
<td>12</td>
<td>Royal Sonesta Harbor Court Hotel</td>
</tr>
<tr>
<td>13</td>
<td>Sheraton Inner Harbor</td>
</tr>
</tbody>
</table>

### Hotel & Travel

Find up-to-date information at [www.toxicology.org/2019](http://www.toxicology.org/2019) | #2019SOT #toxexpo
All hotel accommodations, rates, internet access, and parking pricing are subject to change. Early departures are subject to penalty fees set by the hotels. Although making your reservations outside the SOT hotel block can sometimes be more economical, it decreases the money available to the Society to carry out its strategic goals and may cause the Society to pay attrition fees for unutilized hotel rooms. In addition, the Society is unable to assist you if you have any difficulties with your room reservation, such as the hotel overbooking or misplacing your reservation. SOT depends on the Annual Meeting revenue (hotel room commissions and rebates) to fund other programs throughout the year and to keep future registration fees low. Please assist the Society by making your hotel room reservation through SOT Housing Bureau. Rates shown are for single and double occupancy; additional fees may apply for additional guests. Please note: services offered, taxes, and fees associated with hotel services are subject to change and availability; tax rate 14.75%. Information listed is complete and accurate as of July 1, 2018. Note: checkout times are usually between 11:00 am–1:00 pm; check-in times are usually between 2:00 pm–4:00 pm.

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<table>
<thead>
<tr>
<th>Hotel</th>
<th>Rewards Program</th>
<th>Blocks to Convention Center</th>
<th>Single/Double Rate</th>
<th>Restaurant</th>
<th>In-Room Safe</th>
<th>Complimentary Breakfast</th>
<th>Complimentary Fitness Center</th>
<th>Swimming Pool</th>
<th>Business Center</th>
<th>Complimentary In-Room WiFi</th>
<th>Room Service</th>
<th>Gift Shop</th>
<th>Overnight Self-Parking*</th>
<th>Valet Parking Per Night*</th>
<th>AAA Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Baltimore Marriott Inner Harbor at Camden Yards 110 S. Eutaw Street</td>
<td>Marriott Rewards</td>
<td>2</td>
<td>$223</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$30</td>
<td>N/A</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2) Baltimore Marriott Waterfront 700 Aliceanna Street</td>
<td>Marriott Rewards</td>
<td>10</td>
<td>$223</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$26</td>
<td>$45</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3) Days Inn Inner Harbor 100 Hopkins Place</td>
<td>Wyndham Rewards</td>
<td>1</td>
<td>$169</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$30</td>
<td>N/A</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4) Embassy Suites by Hilton Baltimore Inner Harbor 222 Saint Paul Place</td>
<td>Hilton Honors</td>
<td>6</td>
<td>$185</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>$34</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5) Hampton Inn Baltimore-Downtown/Convention Center 550 Washington Blvd.</td>
<td>Hilton Honors</td>
<td>4</td>
<td>$179</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>$38</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6) Hilton Baltimore (SOT Headquarters Hotel) 401 W. Pratt Street</td>
<td>Hilton Honors</td>
<td>1</td>
<td>$221</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>$30</td>
<td>$43</td>
<td>✓</td>
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<td></td>
</tr>
<tr>
<td>7) Holiday Inn Inner Harbor-Downtown Baltimore 301 W. Lombard Street</td>
<td>IHG Rewards Club</td>
<td>2</td>
<td>$199</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$30</td>
<td>N/A</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8) Hotel Monaco Baltimore, A Kimpton Hotel 2 W. Charles Street</td>
<td>Kimpton Rewards</td>
<td>4</td>
<td>$245 Double; $230 King</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>$40</td>
<td>✓</td>
<td>4</td>
<td></td>
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<tr>
<td>9) Hyatt Regency Baltimore Inner Harbor 300 Light Street</td>
<td>World of Hyatt</td>
<td>1</td>
<td>$229</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$30</td>
<td>$42</td>
<td>✓</td>
<td>3</td>
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<tr>
<td>10) Lord Baltimore Hotel 20 W. Baltimore Street</td>
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<td>2.5</td>
<td>$209</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>$33</td>
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</tr>
<tr>
<td>11) Renaissance Baltimore Harborplace Hotel 202 E. Pratt Street</td>
<td>Marriott Rewards</td>
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<td>$223</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$33</td>
<td>$43</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12) Royal Sonesta Harbor Court Hotel 550 Light Street</td>
<td>Travel Pass</td>
<td>2</td>
<td>$209</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$28.80</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>13) Sheraton Inner Harbor 300 S. Charles Street</td>
<td>SPG</td>
<td>1</td>
<td>$229</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>$28.50</td>
<td>$42</td>
<td>✓</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Rates Subject to Change*
Registration Deadlines

Register by January 11, 2019, to obtain the early-bird rate and to ensure that you receive your registration materials before the meeting. You can register online, via fax, or by mail to SOT Headquarters.

How to Register

Online Registration

SOT members and nonmembers are invited to register for the 2019 SOT Annual Meeting using the SOT Online Registration System. The system is designed for those who will be paying the registration fee by credit card. Registration can be completed via the SOT website at www.toxicology.org/register.

The online registration system will be open throughout the meeting, and if you register online after March 7, 2019, you can easily pick up your badge at the Registration counters on-site.

Confirmation

Online registrants will receive an electronic confirmation following registration. If you do not, please send an email to sotmeetings@toxicology.org. All registrants will be mailed a registration confirmation, name badge, and CE course and/or event ticket(s) before the meeting if the registration form is received by January 11, 2019. If your registration is received after January 11, 2019, you can pick up your badge and tickets at the Registration counters on-site.

Fax or Mail Registration

Registrants may fax or mail their registration payments using the Registration Form. No phone registrations will be accepted.

Forms will be date-stamped as they arrive. This is your date of registration. Fax registrations will be accepted by SOT Headquarters only if a credit card number is clearly listed in the appropriate area. SOT needs only one copy for processing.

DO NOT mail your registration form to SOT if it will arrive after March 7, 2019. SOT will accept Annual Meeting registrations until March 7. After March 7, registrations not processed online will be accepted only on-site at the Annual Meeting.

Early-Bird Registration:

January 11, 2019

Standard Registration:

February 7, 2019

Final Registration:

After February 7, 2019

If mailing, please send registration forms to:

SOT Headquarters
11190 Sunrise Valley Drive, Suite 300
Reston, VA 20191

Fax: 703.438.3113
(Faxes require credit card payment.)
Registration

Payment
One of the following payment methods must accompany registration forms:

- Company or personal check (United States currency only; please list all registrants on check memo or check stub)
- Government Purchase Order (check must be drawn from the US Department of Treasury)
- Money order
- Visa, MasterCard, Discover, Diner’s Club, or American Express

Exhibitor Registration
Exhibitors should register using the Exhibitor Service Center. For assistance with exhibitor registration, please contact Will Low by emailing will@toxicology.org or calling 703.438.3115.

Guest/Spouse Registration
If a nonscientist is accompanying you to the meeting, guest registration is available. You may register your guest while registering yourself for the meeting. If you have already registered for the meeting, complete the Guest Registration Form, marking the appropriate sections for guest registration, and send it to SOT Headquarters along with a copy of your registration confirmation.

The SOT Guest/Spouse Hospitality Room, located at the Hilton Baltimore, provides guest registrants with a place to meet and socialize. The room will be open Sunday through Wednesday.

Reminder: guest registrants and children under age 15 are not permitted in the ToxExpo Exhibit Hall or in Scientific Sessions. Only the Scientific Session chairs can give permission to attend sessions held outside the Exhibit Hall. Please contact David Rossé at davidr@toxicology.org to inquire about obtaining permission in advance.

Media Registration
SOT welcomes accredited representatives of media organizations. See page 28 for more information on media credentialing.

Cancellation, Refund, and Registration Policies
All requests for cancellations and/or refunds must be received in writing at SOT Headquarters by February 7, 2019. These refunds will be processed, less a $50 cancellation fee, following the Annual Meeting. Refund requests received after February 7, 2019, will not be processed. By registering for the 2019 SOT Annual Meeting, you are agreeing to the terms and conditions of the Annual Meeting Policies.

Registration Materials
Badges
Badges and event tickets will be mailed in advance if you register by January 11, 2019. If you need to register or have not received your badge at the time of the meeting, assistance will be available on-site in the Registration area.

NOTE: If you are registered and have your badge, you do not need to enter the Registration line.

Tickets
Tickets are required for CE courses and some other events. If you have these events on your registration form, your tickets will be issued with your meeting badge. Annual Meeting registration is required to participate in CE and other activities.
2019 SOT Annual Meeting Policies

By registering for the 2019 SOT Annual Meeting, you are agreeing to the following terms and conditions:

For individuals who are not members of SOT, participation in SOT’s Annual Meeting and ToxExpo is available only to bona fide individuals who are engaged in or promote the field of toxicology or biotechnology research and support the growth and development of the toxicology field. For organizations, participation in SOT’s Annual Meeting and ToxExpo is available only to bona fide organizations with public policy positions and business practices that are generally consistent with SOT’s mission, goals, reputation, and its policies and principles as determined by SOT. SOT reserves the right to review applications for participation at SOT’s Annual Meeting and ToxExpo to confirm that the applicant meets these criteria and may, at SOT’s sole discretion, reject a registration by any individual or organization or withdraw registration privileges at any time if any individual or organization is found to be inconsistent with SOT’s principles and interests.

Unless written notification by the registrant, stating otherwise, is submitted to SOT Headquarters prior to the Annual Meeting or while registering on-site, SOT Annual Meeting registrants grant SOT permission:

- To reproduce, copy, and publish image, voice, and any or all media taken at the Annual Meeting.
- To share registrant contact information with organizations that SOT believes might have a product or service of interest to you. Limited data provided to third parties include name, affiliation, and business address. Your telephone, fax numbers, and email will not be disclosed to third parties.
- To share registrant name and affiliation with SOT exhibiting companies.
- To be included in the attendee listing accessible to meeting registrants using the SOT Mobile Event App (registrant name and affiliation shared).

SOT Annual Meeting registrants are prohibited from:

- Inviting children under the age of 15 and guest/spouse registrants into the ToxExpo Exhibit Hall. (Session chairs must provide consent for the guest/spouse or child to attend sessions.)
- Soliciting in the ToxExpo Exhibit Hall unless they are a current exhibitor. SOT retains the right to have removed from the exposition any company that has not duly contracted for exhibit space.
- Taking photographs or other electronic capture of Scientific Sessions in meeting rooms or the ToxExpo without the consent of the session chair and the presenter(s)/author(s).
- Photographing colleagues against the backdrop of scientific posters on display without the express consent of the presenting author(s).
- Photographing exhibit booths.
- Speaking on a cell phone while attending Scientific Sessions.

The policies adopted above will be enforced by the Society. Those individuals who do not comply will be asked to leave the session or ToxExpo floor. If you have any questions regarding these policies, please contact the SOT Headquarters Office.
Connect and Network with Scientists

Join the Society of Toxicology (SOT) to engage with more than 8,200 members from 70+ countries and advance toxicology research.

Member Benefits Include:

- **Discounted Registration Rates** for SOT-Hosted Meetings
- **Free or Discounted Access** to *Toxicological Sciences*, the Society’s Official Journal
- **Exclusive Award Opportunities**
- **Career and Education Resources** for all career levels—From Undergraduates to Senior Scientists

**SOT Membership = Annual Meeting $avings**

Apply for SOT membership by December 31 to qualify for discounted registration fees for the 2019 Annual Meeting and ToxExpo. Approved new members will be notified in February 2019.

www.toxicology.org
The SOT 58th Annual Meeting and ToxExpo is taking place at the Baltimore Convention Center, located at 1 West Pratt Street in Baltimore's famed Inner Harbor. The five-day meeting consists of 6,100+ attendees from 50+ countries attending more than 80 Featured and Scientific Sessions, participating in hundreds of hosted events, and interacting with 315+ exhibitors in the three-day ToxExpo.

**General Information**

**On-Site Services**

**Business Center**

Tel: 410.649.7194 | Email: eking@abcimaging.com  
Pratt Street Lobby, across from Room 333

The ABC Imaging Business Center offers services such as shipping via FedEx, DHL, or UPS; common office supplies; and high-quality full-color and black-and-white copying, printing, and uploading of documents from a USB drive.

**Childcare Services**

Contact the concierge at your hotel to make arrangement for childcare services. Children are not permitted in session rooms or the ToxExpo Exhibit Hall.

**Coat/Luggage Check**

A coat/luggage check will be available in the Pratt Street lobby and Charles Street lobby. There will be a fee of $3 per item checked. Laptops, cameras, and other electronics will not be accepted.

Coat/luggage check hours are subject to change.

**Discover Baltimore**

There are many dining, entertainment, and activity options in Baltimore within walking distance of the convention center and SOT hotels. Visit the [SOT Visit Baltimore website](#) for discounts available to meeting attendees, restaurant recommendations, and more.

**Hours of Operation:**

- **Saturday & Sunday**: Closed
- **Monday & Tuesday**: 8:30 AM–4:30 PM
- **Wednesday**: 8:30 AM–7:00 PM
- **Thursday & Friday**: 8:30 AM–4:30 PM

- **Hours of Operation:**
- **Sunday**: 6:30 AM–8:30 PM
- **Monday**: 7:00 AM–6:00 PM
- **Tuesday**: 7:00 AM–6:00 PM
- **Wednesday**: 7:00 AM–6:00 PM
- **Thursday**: 7:00 AM–12:00 Noon
General Information

First-Aid and Emergency Services at the Convention Center

If an emergency should occur at the Baltimore Convention Center, use any beige-colored house phone located around the facility to contact the Public Safety Office or call 410.649.7055. You will be connected directly to the 24-hour public safety dispatcher at the convention center.

A first-aid room will be located in the Pratt Street East Show Office. Please note that in accordance with regulations, the first-aid administrator is not permitted to dispense any medication.

Guest/Spouse Hospitality Room

The SOT Guest/Spouse Hospitality Room will be located in the Hilton Baltimore. The hospitality room provides guest registrants (nonscientists) with a place to meet and socialize with other guests. The room will be open Sunday through Wednesday, and information on local attractions will be available. Guests must register for the Annual Meeting with the person they are accompanying in order to access the hospitality room.

Internet Access at the Convention Center

SOT knows the importance of staying connected to your daily activities while attending the Annual Meeting and ToxExpo and provides several ways for you to access the internet while in the convention center.

Free Wireless Internet Access

SOT will provide free wireless internet access throughout the convention center in all locations where SOT events are being held.

To connect to the free wireless internet, browse the available wireless networks and select the 2019SOT wireless network. Once connected, launch your web browser and click the “proceed” button on the start page. You will then be connected to the SOT welcome splash page and the free wireless network.

@SOT Center—Internet Access

SOT provides computers with free internet access as part of the @SOT Center, located near Registration.

Letter of Attendance

Please stop by Registration starting Tuesday afternoon if you would like a letter of attendance for your participation in the 2019 SOT Annual Meeting and/or the Continuing Education course(s). If you are unable to pick up your attendance letter on-site, you may send your request to sotmeetings@toxicology.org.

Lost and Found

Lost and found articles should be taken to the SOT Headquarters Office, Room 328, in the convention center. Any items left in the office after 11:30 am on Thursday, March 14, will be returned to SOT Headquarters. Information on retrieving posters not claimed by the end of Poster Sessions is available in the FAQs on the Poster Sessions page of the Annual Meeting website.

If you have any questions regarding these policies, please contact the SOT Headquarters office by emailing sotmeetings@toxicology.org.
General Information

SOT Headquarters Office
The SOT Headquarters Office is located in the convention center, Room 328. SOT leadership and staff utilize this office to conduct SOT business while on-site. Visit the office to report or reclaim lost and found items at the convention center.

SOT Pavilion—A Place to Connect
Stop by the SOT Pavilion anytime during ToxExpo hours to connect and catch up with your SOT friends and colleagues. At the Pavilion, you also can:
- Chat with Toxicological Sciences Editor in Chief Gary W. Miller and Managing Editor Virginia Hawkins;
- Reserve a spot or hold a last-minute meeting with colleagues;
- Share your Annual Meeting, SOT, and toxicology experiences as part of the GSLC #YouTox campaign; and
- Learn about SOT activities, programs, and membership.

Hours of Operation:
- Saturday: 4:00 PM–6:00 PM
- Sunday: 7:00 AM–5:30 PM
- Monday: 7:00 AM–5:30 PM
- Tuesday: 7:00 AM–5:30 PM
- Wednesday: 7:00 AM–5:30 PM
- Thursday: 7:00 AM–11:30 AM

Assistance for Speakers and Presenters

Scientific Poster Printing Services
SOT offers poster presenters the ability to have a poster printed and picked up on-site in Baltimore instead of having to carry it to the meeting. Shepard Exposition Services is the official general service contractor providing this service on behalf of SOT. Shepard will have a list of all scientific poster presenting authors and will issue an email to presenters with a link and password to complete the online order. If you are not a scientific poster presenter but wish to have a poster printed, please contact Shepard directly via email at baltimore@shepardes.com.

Orders must be received by February 18, 2019. Please direct questions about this service to baltimore@shepards.com.

Speaker Ready Room
All presenters are strongly encouraged to preload their presentations before traveling to Baltimore for the Annual Meeting. SOT will provide all confirmed Scientific Session presenters with login credentials to access the meeting’s AV portal to remotely load presentations. Links to the AV portal will be available in February 2019. Once in Baltimore, all presenters should visit the Speaker Ready Room (Room 327) to view their presentation and ensure that everything is working properly. If you are unable to preload your presentation, you also may use the Speaker Ready Room to upload your presentation. The Speaker Ready Room will be staffed with experts available to answer any presentation-related questions and address any presentation concerns. Presentations should be loaded and previewed in the Speaker Ready Room—not in the Scientific Session rooms—at least 30 minutes before session start times.

Speaker Ready Room Hours:
- Saturday: 4:00 PM–7:00 PM
- Sunday: 7:00 AM–5:00 PM
- Monday: 7:00 AM–5:00 PM
- Tuesday: 7:00 AM–5:00 PM
- Wednesday: 7:00 AM–5:00 PM
- Thursday: 7:00 AM–10:30 AM
Publications and Media

Media Support Services

SOT welcomes accredited representatives of media organizations to its Annual Meeting. Attending media representatives receive complimentary registration for the meeting, and interviews can be arranged with SOT Council members, meeting speakers and presenters, and SOT members. For more information, please contact Michelle Werts by emailing michelle@toxicology.org or calling 703.438.3115.

The Program

The Program is the official guide to all the activities of the 2019 Annual Meeting and ToxExpo and will be available only as a PDF in 2019. It will be available on the Annual Meeting website in February 2019. All the information available in the Program also will be available on the SOT Mobile Event App, which will be released in February 2019.

The Program includes detailed information on the Scientific Sessions, including the Poster Session schedule and a map of the Poster Sessions, as well as an overview of all the Continuing Education course offerings and a complete schedule of the Annual Meeting events and activities.

Scientific ePosters

SOT is pleased to offer poster presenters the opportunity to share their research electronically as well as during their assigned Poster Sessions. Poster presenters will be able to upload their ePosters beginning in February 2019. ePosters will be available to meeting attendees through the SOT Mobile Event App and Online Planner until May 15, 2019.

SOT Mobile Event App

The SOT Mobile Event App, launching in February 2019, is your all-in-one resource for the SOT Annual Meeting and ToxExpo. Contained within the SOT Mobile Event App is information on the Scientific Sessions, abstracts for the 2,100+ presentations, and details on the 315+ ToxExpo exhibitors. With the app, attendees can:

» Search the complete schedule by presentation, keyword, speaker, or organization to view all meeting abstracts and event descriptions;
» Create a customized schedule by adding individual events, presentations, posters, or sessions to their calendar; and
» Plan their ToxExpo experience by accessing floor maps and exhibitor lists.

Looking to access app content before February 2019? Use the SOT Online Planner on the SOT website to view session descriptions, customize your schedule, and more. Any personalization you complete with the Online Planner, such as saving favorites or adding sessions to your schedule, will automatically sync with the SOT Mobile Event App.

The Toxicologist

The Toxicologist is the official compilation of all accepted abstracts for the SOT 58th Annual Meeting and will be available only as a PDF in 2019. With more than 2,100 abstracts for the meeting, this supplementary issue of Toxicological Sciences is a critical scientific record of the latest findings in toxicology and will be published as a PDF on the Annual Meeting website in February 2019.

Late-breaking abstracts will appear in a separate, PDF-only publication, The Toxicologist: Late-Breaking Supplement, which will be available on the Annual Meeting website in March 2019.
Events and Activities

All activities will be held at the Baltimore Convention Center, unless otherwise noted.

Welcome Reception
Sunday, March 10, 6:30 PM to 7:30 PM
The Welcome Reception is a great opportunity to renew friendships and to make new acquaintances. Please join the Society in this kickoff of the Annual Meeting.

25-Year (Or More) Member Reception
Sunday, March 10, 7:00 PM to 8:00 PM
If you have been a member of the Society of Toxicology for 25 years or more, please join your colleagues in recognition and celebration of your contributions to the Society. Be sure to wear your membership anniversary pin.

Global Gallery of Toxicology
Monday, March 11 to Wednesday, March 13, 9:15 AM to 4:30 PM
Toxicology societies from around the world are invited to participate in the Global Gallery of Toxicology, now in its eighth year. Posters of these sister societies will be prominently displayed during the meeting, showcasing these societies’ key accomplishments, strategic initiatives, and activities. Meet representatives of these organizations from 11:45 am to 12:15 pm on Monday, March 11. Posters will be available for viewing during the ToxExpo hours. For more information about participating in the Global Gallery, please contact Kevin Merritt by email at kevin@toxicology.org by January 4, 2019.

Regional Chapter, Special Interest Group, and Specialty Section Posters
Monday, March 11 to Wednesday, March 13, 9:15 AM to 4:30 PM
Dedicated poster space is available for the SOT Regional Chapters, Special Interest Groups, and Specialty Sections during the 2019 SOT Annual Meeting. The poster area will be located adjacent to the SOT Pavilion in the ToxExpo Exhibit Hall. Come meet representatives on Monday, March 11, from 11:45 am to 12:15 pm. Posters will be available for viewing during the ToxExpo hours.
Global Collaboration Coffee

**Monday, March 11, 9:30 AM to 11:30 AM**

IUTOX invites all Global Gallery participants and representatives of societies from around the world to the Global Collaboration Coffee, hosted by SOT. This event offers an opportunity for scientific leaders to connect and gain a better understanding of the initiatives of societies around the world. Following the coffee, attendees will adjourn together to the Global Gallery, where presenters will share their posters in a “Representative Attended” poster time from 11:45 am to 12:15 pm on Monday, March 11. Please see the previous page for additional information about the poster display. Please contact Kevin Merritt by email at kevin@toxicology.org for participation information on the Global Collaboration Coffee and Global Gallery.

SOT Mentoring Breakfast

**Monday, March 11, 6:15 AM to 7:45 AM**

*(Ticket Required)*

**Endorser(s):** Career Resource and Development Committee, Postdoctoral Assembly, Graduate Student Leadership Committee

The Society of Toxicology recognizes the importance of mentoring in the scientific and professional development of its members. Therefore, the Society is pleased to announce the eighth annual Mentoring Breakfast.

The Mentoring Breakfast is for SOT members at any career stage—from students and scholars to senior scientists—who are seeking a mentor. Trained facilitators will lead small-group discussions to determine each individual’s wants and needs in a mentor and then will use this information to connect the participant with an appropriate mentor. Please note that mentor information will be provided after the Annual Meeting and that mentors do not attend the breakfast.

Registration is limited and is accepted on a first-come, first-served basis. Attendance cost is $10 per person and includes a continental breakfast.

Research Funding Insights

**Monday, March 11, 9:30 AM to 3:00 PM; Tuesday, March 12 and Wednesday, March 13, 9:30 AM to 4:30 PM**

**Hosted by:** Career Resource and Development Committee

Representatives from federal agencies will be available in the Research Funding Insights Room for individual conversations. Make an appointment with your program officer in advance or check the posted schedule to meet with a staff member who can discuss aspects of scientific review or specific grant opportunities. New investigators are especially encouraged to meet with program staff.

Past Presidents’ 5K Fun Run/Walk

**Tuesday, March 12, 7:00 AM, Camden Yards Sports Complex**

**Supported by:** IDEXX BioAnalytics

When you pack for the meeting, don’t forget your running shoes so you can participate in the ninth annual Past Presidents’ 5K Fun Run/Walk! Open to anyone interested, this event is a great opportunity to meet friends and make new acquaintances in a casual environment, joining SOT Past Presidents in showing support for the Society. Whether you’re in it for some friendly competition or would rather take a leisurely stroll, this event’s emphasis is on camaraderie and will bring together runners and walkers of all levels and paces.

Register by February 4, 2019, to receive a complimentary souvenir T-shirt; visit the Program Details page of the SOT Annual Meeting website to register. Registration is only $25, and all proceeds support the SOT Endowment Fund.
Events and Activities

**SOT Annual Business Meeting**

**Tuesday, March 12, 4:45 PM to 6:15 PM**

SOT members are invited and encouraged to attend the Annual Business Meeting. The agenda includes a financial summary, a review of the 2018–2019 accomplishments, and highlights of the new strategic plan.

**Tox ShowDown**

**Tuesday, March 12, 7:30 PM to 9:00 PM, Location to Be Announced**

**Chairperson(s): Phil Wexler, Bethesda, MD.**

This is the eighth year of the Tox ShowDown, the toxicological quiz game par excellence. Three teams of three contestants each—the Endocrine Disruptors, the Free Radicals, and the Toxic Metabolites—battle each other to answer questions wholly, partially, or remotely related to toxicology. Topics run the gamut, including the role of toxicology in history, current events, arts, culture, and society, not to mention science. The event features a cash bar and is a great opportunity to see how many questions you can answer correctly while enjoying a good laugh.

**Undergraduate Educator Network Meeting**

**Date and Time to Be Announced**

**Chairperson(s): Christine Perdan Curran, Northern Kentucky University, Highland Heights, KY.**

**Endorser(s): Education Committee, Undergraduate Education Subcommittee**

The Undergraduate Educator Network Meeting is for all faculty involved in teaching toxicology to undergraduates, trainees thinking about teaching, and those interested in including toxicology at the undergraduate level. Learn about initiatives for undergraduate faculty, provide your input, network with your colleagues, and discuss shared interests.

**Regional Chapter, Special Interest Group, and Specialty Section Events**

Throughout the SOT Annual Meeting and ToxExpo, the SOT Regional Chapters, Special Interest Groups, and Specialty Sections host a variety of activities, including:

- Breakfasts, luncheons, and evening receptions;
- Mentoring and career events; and
- Student- and postdoctoral-focused events.

These events are open to all meeting attendees, regardless of membership with the hosting group.

Information on SOT Regional Chapter, Special Interest Group, and Specialty Section events is continually updated and added to the SOT Annual Meeting schedule. Visit the [Program Details page](#) on the SOT website for the most up-to-date schedule of events and descriptions.
**Students and Postdoctoral Scholars**

**Undergraduate Diversity Program**

**Saturday, March 9 to Monday, March 11, Various Locations**

*Chairperson(s):* Irene Abraham, JT International, Geneva, Switzerland; and James Luyendyk, Michigan State University, East Lansing, MI.

*Hosted by:* Committee on Diversity Initiatives (CDI)

Recipients of the Undergraduate Diversity Program Student and Advisor Travel Awards participate in a three-day program to learn more about toxicology and careers in biomedical research. This year, we are celebrating the 30th anniversary of this initiative! The program begins Saturday evening with networking in mentoring groups, an introduction to toxicology, and the CDI Reunion, a celebration including current and past program participants and organizers. Everyone is invited to attend! See the description below for the Sunday activities. On Monday, these students participate in Scientific Sessions, visit posters, and attend the *In Vitro* Toxicology Lecture and Luncheon for Students. Participants continue to network with toxicologists and have a special session to conclude this concentrated exposure to toxicology and opportunities after graduate studies in the biomedical sciences. For schedule details, go to the [Program Details page](#) of the SOT Annual Meeting website.

**Committee on Diversity Initiatives Reunion**

**Saturday, March 9, 7:30 PM to 8:30 PM, Hyatt Regency Baltimore**

*Hosted by:* Committee on Diversity Initiatives (CDI)

Join the CDI as we celebrate the 30th anniversary of the Undergraduate Diversity Program and the people who make it successful. The CDI Reunion is a great opportunity for former students, organizers of the program, and volunteers to gather and celebrate 30 years of success in encouraging the next generation of scientists. Please welcome and network with this year’s undergraduate student participants and mentors. The program will include the presentation of the 2019 Perry J. Gehring Diversity Student Travel Award. Dessert, coffee, and tea will be served. Please mark your calendars and begin the 58th Annual Meeting with this important and exciting recognition of this milestone.

**Sunday Undergraduate Education Program**

**Sunday, March 10, 8:00 AM to 5:00 PM, Hyatt Regency Baltimore**

*Chairperson(s):* Irene Abraham, JT International, Geneva, Switzerland; and James Luyendyk, Michigan State University, East Lansing, MI.

*Hosted by:* Committee on Diversity Initiatives (CDI)

*Endorser(s):* Education Committee, Undergraduate Education Subcommittee

Undergraduates participate in this special introduction to topics in various toxicology disciplines, including an opportunity to explore and interpret data. Students discuss with graduate students and academic program directors how to submit strong graduate school applications and succeed in graduate school, as well as learning the merits of specific graduate programs. They also network with SOT mentors and toxicologists in various employment sectors to become more familiar with what life is like in different career paths in toxicology. For schedule details, go to the [Program Details page](#) of the SOT Annual Meeting website.
**Student/Postdoctoral Scholar Mixer**

**Sunday, March 10, 7:30 PM to 9:00 PM, Hilton Baltimore**

*(Ticket Required)*

**Hosted by: Graduate Student Leadership Committee (GSLC)**

This is an opportunity for all students and postdoctoral scholars to gather, meet new colleagues, and reestablish relationships in an informal atmosphere at the beginning of the meeting. Learn about being involved in SOT by speaking with student leaders at the SOT component group posters. The GSLC Outstanding Leadership Award is presented during this event. Tickets are obtained at no cost by registering for the mixer on the Annual Meeting registration form. A ticket and meeting badge are required. Complimentary refreshments and a cash bar will be available.

**Chat with an Expert**

**Monday, March 11 to Thursday, March 14, Time Varies by Group**

*(Meet at the Chat with an Expert Poster Board in the Main Lobby)*

**Hosted by: Graduate Student Leadership Committee (GSLC)**

The purpose of Chat with an Expert is to provide graduate students and postdoctoral scholars with the opportunity to network informally with well-established toxicologists while obtaining career advice and meeting new colleagues. Small groups are formed by matching research interests of students and postdocs with those of an expert. The expert for each group identifies a time and a place for an informal meeting, and the group meets at the Chat with an Expert Poster before proceeding to the meeting location. This program also includes opportunities for postdocs to host informal meetings with graduate students during the Chat with a Postdoc portion of the program. Expert registration is open until January 11; graduate student/postdoc registration will open in early 2019. Details for each group meeting will be sent to participants in advance.

**Poster Tours for Trainees**

**Monday, March 11 to Wednesday, March 13, Time Varies by Group**

*(Meet at the Poster Tour Board in the Pratt Street Lobby near Registration)*

**Hosted by: Postdoctoral Assembly (PDA)**

The Postdoctoral Assembly organizes Poster Tours for Trainees for graduate students and postdoctoral scientists to participate in a one-hour guided poster tour with an expert toxicologist. These small group tours provide the opportunity for trainees to take part in critical evaluation of cutting-edge toxicology methods and research findings and network with an expert toxicologist. Recruitment of individuals interested in being poster tour guides begins in early December. Graduate student and postdoctoral scholar sign-up will open in early 2019. Details for each group will be distributed to the participants in advance.

**Trainee Discussion with Plenary Session Presenter: Dr. Murphy**

**Monday, March 11, 9:45 AM to 10:45 AM**

*(Ticket Required; Limited Seating)*

**Presenter: William L. Murphy, University of Wisconsin-Madison, Madison, WI.**

Dr. Murphy will meet informally for discussion with graduate students and postdoctoral scholars after the Plenary Session Lecture. Registration is limited to SOT student and postdoctoral members.
**In Vitro Toxicology Lecture and Luncheon for Students**

Patient-Based Cellular Model Systems to Assess Individual Risk to Neurotoxicants

**Monday, March 11, 12:00 Noon to 1:30 PM, Hilton Baltimore**

(Ticket Required)

**Chairperson(s):** Deb Hoivik, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; and Agnes Karmaus, ILS, Research Triangle Park, NC.

**Lecturer:** Aaron B. Bowman, Purdue University, West Lafayette, IN.

**Supported by:** An Educational Grant from the Colgate-Palmolive Company

**Hosted by:** Education Committee

The goal of the *In Vitro Toxicology Lecture series* is to feature important research using *in vitro* and alternative techniques to study basic mechanisms and to develop test methods aimed at replacing animal use whenever feasible. Undergraduate students, graduate students, postdoctoral scholars, and recipients of Colgate-Palmolive awards are among the guests at this event. Students and postdoctoral scholars register for $10 (nonrefundable) with their Annual Meeting registration. Lunch service is available for guests with tickets who arrive before 12:15 pm. After lunch, the speaker makes a short presentation, which is the basis for a case study discussion at each table.

Dr. Bowman will examine the benefits of using induced pluripotent stem cells (iPSC) technology to personalize human risk assessment for suspected and known neurotoxicants. iPSCs can be generated from individual human subjects or representative vulnerable populations. These cells can be used to differentiate cells along all three embryonic germ lines, including the brain and neurovascular unit. Examples from the recent literature will be used to illustrate opportunities and challenges in the field. The audience will be asked to discuss these opportunities and challenges and apply their ideas to a real-world situation.

**Postdoctoral Assembly Luncheon**

**Tuesday, March 12, 12:00 Noon to 1:00 PM**

(Ticket Required)

**Chairperson(s):** Manushree Bharadwaj, NIEHS, Research Triangle Park, NC.

**Hosted by:** Postdoctoral Assembly (PDA)

The Postdoctoral Assembly Luncheon is a casual event that encourages engagement and networking among postdoctoral scholars. Finishing up a discussion from your morning poster session? Leaving early to set up a poster or attend another meeting? That’s no problem; stop in when you can! Enjoy a buffet lunch while networking with others, including PDA officers, Postdoctoral Representatives, and SOT Council members. This is the time for postdocs to relax, celebrate achievements, and have fun. At 12:30 pm, there will be a short program, which will include recognizing the Best Postdoctoral Publication Award recipients and welcoming of 2019–2020 PDA officers. Door prizes add even more fun to this lively event. Postdocs should reserve a ticket for $10 when registering for the Annual Meeting.
Career Exploration through Speed Informational Interviews

**Tuesday, March 12, 1:30 PM to 2:50 PM**

*(Ticket Required)*

**Hosted by: Postdoctoral Assembly (PDA)**

Do you find yourself wondering what your career options are in the field of toxicology? Then this is the event for you! This career development special event is designed for graduate students and postdocs who want to gain insight into the different career sectors in toxicology. Groups of trainees will rotate through a series of approximately eight-minute discussions with career representatives from academia, government, and industry. Trainees can ask the career representatives questions about their background, their career path, the hiring process in their company/sector, and other aspects of identifying and pursuing career interests. This session will provide an informal opportunity to gain insight into different employment sectors in toxicology through candid discussions in a casual setting. Graduate students and postdocs are encouraged to register early, as registration will be limited to maximize the opportunity for small-group discussion with career representatives.

Trainee Discussion with Medical Research Council (MRC) Lecturer: Dr. Lord

**Wednesday, March 13, 2:00 PM to 3:00 PM**

*(Ticket Required; Limited Seating)*

**Lecturer: Janet M. Lord, University of Birmingham**

**Institute of Inflammation and Ageing, Birmingham, United Kingdom.**

Dr. Lord will meet informally for discussion with graduate students and postdoctoral scholars after her Keynote MRC Lecture. Registration is limited to SOT student and postdoctoral members.

Undergraduate Student Meeting

**Date and Time to Be Announced**

**Chairperson(s):** Blase Billack, St. John’s University, Jamaica, NY; Gunnar Frances Kwakye, Oberlin College, Oberlin, OH; and Christine Perdan Curran, Northern Kentucky University, Highland Heights, KY.

**Hosted by: Education Committee, Undergraduate Education Subcommittee**

An informal session for all undergraduate students attending the SOT Annual Meeting will be hosted by the Undergraduate Education Subcommittee. SOT undergraduate travel awardees are expected to participate. Peer into your toxicology future by connecting with your peers, graduate students, and postdoctoral scholars with common interests in the science of safety and career opportunities in the field. This session will include opportunities for networking with toxicology professionals and career development along with free refreshments for all participants.
Continuing Education Courses

The Continuing Education (CE) Program offers a wide range of courses that cover established knowledge in toxicology, as well as advanced techniques or approaches for those with experience in the field. Courses can be applied toward certifying and licensing board requirements and also may be used for recertification with the American Board of Toxicology (ABT). General courses are intended to provide a broad overview of an area or to assist individuals in learning new techniques or approaches, while courses based on more specialized topics are intended to be of interest to individuals with previous knowledge of the subject or already working in the field.

All courses will be held at the Baltimore Convention Center. Please check the signage in the Registration area and at the CE booth for room assignments. Note: links to the electronic CE course books are distributed before the meeting; USB drives containing electronic copies of the CE course books will be available in the room immediately prior to the course (they will not be available at the Registration area).

Registration for the Annual Meeting and a separate CE course ticket are required.

Handling Uncertainties in Evaluating Mixtures: What’s the Difference between a “Similar” and a “Sufficiently Similar” Mixture?

Sunday, March 10
SR—Sunrise (7:00 AM–7:45 AM)
AM—Morning (8:15 AM–12:00 Noon)
PM—Afternoon (1:15 PM–5:00 PM)

Chairperson(s): Suzanne Fitzpatrick, US FDA, College Park, MD; and Mansi Krishan, Danone North America, Louisville, CO.

Primary Endorser: In Vitro and Alternative Methods Specialty Section
Other Endorser(s): Risk Assessment Specialty Section; Women in Toxicology Special Interest Group

Evaluating the safety and potential health risks from exposure to multiple chemicals, such as environmental chemicals, pharmaceuticals, consumer and personal care products, and pesticides and food contaminants, poses one of the major challenges for toxicological research and risk assessment. Significant advances have been made in recent years in better understanding and evaluating chemical mixtures. A key factor in risk assessments of chemical mixtures is the availability of reliable data on the identity, levels of exposure,
toxicokinetics, toxicodynamics, and toxicological interactions for the whole mixture or its individual components. Limited data or lack of data has a direct impact on uncertainty of the risk assessment of mixtures. As a result, risk assessment of chemical mixtures requires a lot of assumptions and uncertainty assessment. The commonly used risk assessment methods for chemical mixtures are whole mixture approaches and component-based approaches. The whole mixture approach is used when toxicological data are available for the mixture itself or toxicity data are available for a similar mixture or a sufficiently similar mixture that can be used as surrogate for the mixture of concern. This CE course will (1) provide an overview of challenges related to whole mixtures risk assessment and highlight approaches for evaluating sufficient similarity among related mixtures, and (2) present recent advances in safety assessment of complex mixtures using an alternative tiered approach, which utilizes in silico and in vitro approaches to identify safety data gaps and inform the need for additional studies. Attendees will be equipped to use similarity and sufficient similarity for whole mixtures, understand the assumptions, and understand how to address the uncertainties. This course would be of interest to scientists who conduct mixtures risk assessment in different sectors, such as occupational health and safety, product safety, public health protection, or regulatory decision-making. This sunrise CE course complements the previous CE courses and sessions at SOT on mixtures and focuses specifically on the uncertainty assessment aspect of similar and sufficiently similar mixtures, which has not been discussed before.

**Assessing Human Health Risks from Whole Chemical Mixtures: An Overview.** Glenn Rice, US EPA, Cincinnati, OH.

**Novel Uncertainty Assessment Approaches for Evaluating Mixture of Concern, Sufficiently Similar Mixtures, or Similar Mixtures, Using Case Studies.** Amy Roe, Procter & Gamble Company, Cincinnati, OH.

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**Publicly Available Exposure Tools to Inform the Toxic Substances Control Act**

**Sunday, March 10, 7:00 AM to 7:45 AM**

**SR02 | Sunrise Mini-Course**

**Chairperson(s):** John Wambaugh, US EPA/NCCT, Research Triangle Park, NC; and Kristin Isaacs, US EPA/NERL, Research Triangle Park, NC.

**Primary Endorser: Exposure Specialty Section**

**Other Endorser(s):** Risk Assessment Specialty Section; Specialty Section Collaboration and Communication Group

Exposure is a key component of chemical risk assessments, as highlighted by the recent amendment to the Toxic Substances Control Act mandating the US EPA to consider conditions of chemical use, as well as human and ecological exposures across the chemical life cycle. The US EPA Office of Research and Development has many ongoing exposure modeling efforts that may be informative for chemical safety decisions. This sunrise CE course covers how 21st-century exposure science tools could be used to inform chemical risk assessments. The first instructor will present a series of databases and models that are both peer reviewed and free to use. The second instructor will cover new, consensus exposure predictions for instances where minimal exposure data are available. Each lecture will provide examples that can be easily modified by course attendees for specific chemical risk assessment applications.

**Publicly Available Exposure Data and Models.** Kristin Isaacs, US EPA/NERL, Research Triangle Park, NC.

**High-Throughput Exposure Forecasting.** John Wambaugh, US EPA/NCCT, Research Triangle Park, NC.
Toxicological research and testing heavily depends on the application of cell and molecular assays to provide mechanistic insight into the effects of chemical exposures as well as model systems to overcome the constraints of in vivo human and animal exposure studies. Despite being powerful tools, these assays are not immune from the “reproducibility crisis” that has cast a considerable shadow over all fields of biomedical research. Improving the rigor, reproducibility, and physiological relevance of both traditional and high-throughput cellular and molecular methods is critical to protect human health, increase the efficiency of drug and consumer product development, and ensure the reliability of data used in chemical regulation. Recent reports in both the scientific and public literature have revealed a need for increased rigor in preclinical research and highlighted experimental design, reagents (including antibodies and cell lines), and data analysis as key challenges to study reproducibility. The goal of this course is to provide participants with “good research practices” for the rigorous development, optimization, implementation, and interpretation of robust in vitro toxicological assays for reproducible results using physiologically relevant models. Presentations will follow a broadly applicable workflow, starting with the establishment of a verified cell culture model with increased physiological relevance. Participants will learn how understanding the nature of cells in vitro and treating cells as reagents can ensure the design of more reproducible assays. Strategies will also be shared for the successful implementation of high-throughput assays that enable the rapid and high-throughput assessment of both toxicity and efficacy using in vitro models with increased physiological relevance. This will be followed by global gene expression analysis using RNA sequencing, validation, and exploration of target gene expression with quantitative PCR, assessment of protein abundance, and post-translational modification using immunoassays, and evaluation of cumulative effects of exposures on cell physiology and viability. The final presentation will empower participants with the knowledge and tools to utilize innovative statistical measures that were developed specifically to enable reliable assessments about compound properties based on data from in vitro assays. This course will provide attendees with core principles and practices for widely used methods, which will facilitate the design and execution of a broad range of rigorous and reproducible experiments, increased throughput, and improved in-depth interpretation of data from both study findings and published literature. The content of this course will benefit researchers from industry, government, and academic labs who evaluate the safety of experimental compounds and wish to learn more about the latest models, methodologies, and analysis strategies.

Introduction to the Course. Nathan P. Coussens, NIH/NCATS, Bethesda, MD.

Simple Approaches to Improving Relevance and Reproducibility in Cell Culture. Shaun D. McCullough, US EPA, Chapel Hill, NC.

Treating Cells as Reagents to Design Reproducible In Vitro Toxicology Assays. Terry Riss, Promega Corporation, Madison, WI.

In Vitro Toxicological Testing in qHTS Format. Menghang Xia, NIH/NCATS, Bethesda, MD.

Seq-ing the Truth: Principles and Practices for Quantifying Gene Expression Using RNA Sequencing and Quantitative PCR. Elizabeth Martin, NIEHS, Research Triangle Park, NC.

Maximizing Sensitivity, Reproducibility, and Interpretability of Immunoblots and Immunoassays. Kevin Janes, University of Virginia, Charlottesville, VA.

Characterizing Reproducibility and Optimizing Value of In Vitro Screening Methods. Viswanath Devanarayan, University of Illinois at Chicago, Chicago, IL.
A complex mixture, as defined in a 2018 update to the Agency for Toxic Substances and Disease Registry Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors, has many chemicals (often of different chemical classes), has a composition which may not be fully characterized, and can arise from a single source or multiple sources. The related, but more specifically defined, term, UVCB substances (Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials), has been applied by both the US EPA in the Toxic Substances Control Act (TSCA) Chemical Substance Inventory and the European Chemicals Agency (ECHA) under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations. Complex mixtures and UVCBs can include foods and beverages, personal care or consumer products, reaction by-products, emissions, and leachates. They can exhibit a wide array of physicochemical properties and fall under different regulatory jurisdictions. However, there are common principles that can be applied to these substances to gain an understanding of their complex chemistry and evaluate their toxicity and/or safety. Historically, the prevailing dichotomy was to either treat these substances as single entities, thereby ignoring their complex and often dynamic nature, or apply a reductionist approach that only considered a small subset of known constituents (i.e., identified chemical constituents with available toxicity data). Progress in analytical chemistry techniques, untargeted analyses, and in vitro screening tools has allowed for a more comprehensive and holistic approach to complex mixtures. In this course, state-of-the-science approaches for evaluating complex mixtures and UVCBs will be presented. It will begin with a presentation of the regulatory challenges and views of complex mixtures from the perspective of the US FDA Center for Food Safety and Applied Nutrition (CFSAN). Next, recommended methods for chemically analyzing complex mixtures and identifying biologically active constituents will be presented. Untargeted approaches for assessing complex mixtures, such as metabolomics and chemometrics, will be addressed. The use of in vitro assays and alternative animal models in screening complex mixtures will be discussed, with attention on successful applications and pitfalls to avoid. Additionally, available methods and software for combining chemical and biological assay data will be presented. Finally, existing methods for comparing across complex mixtures and determining sufficient similarity of related mixtures will be presented. Presentations will address chemistry, biological activity, and the intersection of the two, with an intentional focus on how these data can be used in safety evaluations of complex mixtures. Throughout the course, speakers will provide terminology and definitions and highlight tools using a diverse array of examples, representing distinct categories of complex mixtures and UVCBs. This course will be useful to those interested in understanding complex mixtures from a product development, research, or regulatory perspective. Course participants will be provided with both big picture context on complex mixtures and specific recommendations learned from application of the presented methods.
Developmental Toxicity of the Skeletal System: Interpretation of Findings in DART Studies and Implications for Risk Assessment

Sunday, March 10, 8:15 AM to 12:00 Noon
AM05 | MORNING COURSE

Chairperson(s): Michael Garry, Exponent, Inc., Seattle, WA; and AtLee Watson, NIEHS/NTP, Research Triangle Park, NC.

Primary Endorser: Reproductive and Developmental Toxicology Specialty Section

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section

Skeletal development represents a period of rapid patterning and specification of tissues that form the basis for subsequent growth in the developing organism. As a result, formation of the skeletal elements (e.g., bone and cartilage) is included as a standard endpoint in prenatal developmental toxicity studies. Abnormal findings are classified as variations or malformations; however, the interpretation of these findings and whether they result in functional deficits in postnatal life can have significant consequences within a regulatory framework for new compounds coming to market. The goal of this course is to provide participants with an introduction to skeletal anatomy and physiology that can facilitate the interpretation of abnormal findings from a toxicological perspective. Speakers from academia, industry, and government with expertise in the fields of skeletal biology and developmental toxicology will provide (1) a fundamental review of skeletal development in animal models currently used in developmental toxicity studies, with an emphasis on differences in developmental course and extrapolation between species; (2) a discussion of current and emerging methods to identify skeletal anomalies in prenatal and postnatal/juvenile developmental toxicity studies, and their relation to overall developmental toxicity, both in the animal models and their potential human relevance; (3) case studies to illustrate the concepts introduced by the first two speakers and specific challenges faced in the interpretation of study results; and (4) context from a regulatory perspective on the interpretation of abnormal skeletal findings and the evolving requirements needed to address skeletal toxicity concerns.

Introduction. AtLee Watson, NIEHS/NTP, Research Triangle Park, NC.

Skeletal Development in Laboratory Mammals and Humans. John DeSesso, Exponent, Inc., Alexandria, VA.

Interpretation of Skeletal Anomalies in Laboratory Animals. Anthony Scialli, Scialli Consulting, LLC, Washington, DC.

Case Studies of Common Skeletal Findings in Developmental Toxicity Studies. Donald Stump, Charles River Laboratories, Mansfield, OH.


Industrial Applications of Computational Toxicology in the 21st Century

Sunday, March 10, 8:15 AM to 12:00 Noon
AM06 | MORNING COURSE

Chairperson(s): Catrin Hasselgren, Genentech, Inc., South San Francisco, CA; and Alessandro Brigo, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Primary Endorser: Computational Toxicology Specialty Section

Other Endorser(s): In Vitro and Alternative Methods; Risk Assessment Specialty Section

Computational toxicology encompasses the development of computational models and tools applied to datasets of toxicological concern and the use of such methods for various applications. This is a wide field spanning hazard identification, prioritization for experimental testing, optimization of chemical space, and chemical risk assessment. These methods are used in many different industry sectors, such as consumer products, pharmaceuticals, and agrochemicals, as well as being widely used in the environmental sector and in governmental or regulatory organizations. The methods employed vary from simple to complex depending on availability and quality of
data, and range from the application of structural alerts to machine-learning models of large-scale biological data and complex systems toxicology modeling. With increased pressure to reduce the number of animal experiments, accelerate the product development cycles, and lower costs, computational toxicology is a continuously developing area with yet-un tapped potential. This course will give a short background and introduction to the field, followed by a methods section where different scenarios will be presented that guide the participants in how data are analyzed and models and tools are built, depending on the use case at hand, as well as data limitations. This will be followed by two presentations on practical applications of computational toxicology, the first one focused on consumer products (e.g., food, cosmetics) and the second on examples from the pharmaceutical industry. Both of these presentations will highlight the diversity of use cases within each industry. The course will end with a presentation discussing the regulatory landscape and examples of how such tools are used to support regulatory safety assessment of various products. The aim of this course is to introduce the discipline of computational toxicology to the nonexpert and provide the participants with a broad understanding of the many benefits of computational toxicology methods, as well as an understanding of the limitations and appropriate use of such methods for successful outcomes in an industrial setting. The learnings from this course are relevant for attendees from all industry sectors as well as from other research-dedicated organizations.

Computational Toxicology—Past, Present, and Future. Catrin Hasselgren, Genentech, Inc., South San Francisco, CA.

Methods and Principles of Computational Toxicology—The Basics. Nigel Greene, AstraZeneca, Waltham, MA.


Role of Toxicokinetics in Human Health Safety Assessments

Sunday, March 10, 8:15 AM to 12:00 Noon
AM07 | MORNING COURSE

Chairperson(s): Sabitha Papineni, Corteva Agriscience, Indianapolis, IN; and Anna Lowit, US EPA, Washington, DC.

Primary Endorser: Risk Assessment Specialty Section

Other Endorser(s): Biological Modeling Specialty Section; Comparative and Veterinary Specialty Section

Regulatory toxicity testing and risk assessment paradigms historically have been based on external doses, despite acknowledged scientific advantages in using systemic exposures. Integrating toxicokinetics (TK) into regulatory toxicity testing provides an opportunity to develop more relevant data by utilizing systemic dose in animals and predicted (modeled) or measured blood levels of chemicals in humans. This provides a foundation for improved evaluation of human relevance, life-stage susceptibility, mode-of-action or adverse outcome pathway, route-to-route extrapolation, and dose selection. In addition, there is increased emphasis on improving toxicity testing and safety assessment in alignment with the 3Rs principle of animal welfare (replace, reduce, refine), and expanded use and collection of TK information reduces the overall use of animals by eliminating unnecessary or redundant tests and provides more humane dose selections, which are less physiologically stressful on the animals. As with any effort, the challenge lies in harmonization of these approaches across the globe. Increased awareness and communication of the benefits of these approaches is key for global harmonization. This course aims to increase knowledge on the principles of TK and will enable students to explore the opportunities that TK offers to risk assessment (all steps: hazard identification, dose-response assessment, exposure assessment, risk characterization) and provide a forum for students to hear from scientists of varying backgrounds and sectors—regulatory, academic, and industry. There have been many advancements in technology and increased emphasis by regulatory agencies to collect TK data. However, the implementation and applicability of these data in regulatory toxicity testing have lagged considerably. The first talk will introduce the topic and present the basic principles of TK, and also will provide an understanding of why and when TK is useful for investigating issues in toxicology. The second presentation will review the experience of integrating and utilizing knowledge of TK in preclinical safety testing of pharmaceuticals. The third presentation will describe the standard testing protocols, technical details, and considerations to integrate TK in standardized guideline studies without use of additional animals and making the guidelines relevant to assessing risks to human
health. The fourth presentation will describe the view of the European Food Safety Authority (EFSA) on integration of TK in safety assessments and also will discuss all the available tools, using relevant case studies. The final presentation will provide a regulatory overview of integration of TK into various steps in the risk assessment process, using case studies to demonstrate how TK data have been used in pesticide risk assessment to improve the science underlying regulatory decision-making. Overall, this course will provide the needed background and approaches to implement TK, using practical examples that will enable the attendees to have a better appreciation of its utility in risk assessment of and decision-making regarding chemicals for human health. This course also will highlight the shift toward utilization of high-throughput toxicity screening and nonanimal methods that both are in alignment with 3Rs principle and offer cost- and resource-effective means to prioritize chemicals. Thus, this course will be of a broad interest to testing laboratories, general toxicologists, and risk assessors across different sectors, including academia, regulatory agencies, and industry.

An Introduction to Toxicokinetics. Curtis Klaassen, University of Kansas College of Medicine, Kansas City, KS.

Pharmaceutical Industry View of Toxicokinetics. Emile Chen, GlaxoSmithKline, plc, Chester Springs, PA.

Integration of Toxicokinetics in Toxicity Studies. Sabitha Papineni, Corteva Agriscience, Indianapolis, IN.


Mechanistic Understanding and Quantitative Risk Assessment in Immunotoxicology

Sunday, March 10, 8:15 AM to 12:00 Noon
AM08 | MORNING COURSE

Chairperson(s): Emanuela Corsini, Università degli Studi di Milano, Milan, Italy; and Jamie DeWitt, East Carolina University, Greenville, NC.

Primary Endorser: Immunotoxicology Specialty Section

Considering the important health consequences associated with exposure to immunotoxic compounds, quantitative risk assessment in immunotoxicology is an area of growing interest. The discipline of immunotoxicology has refined several powerful tools to assess the safety of new drugs and other products. Novel approaches for assessment of hypersensitivity and cytokine-based assays to examine chemical-specific effects are moving the field away from the use of animals and providing a path forward for hazard identification and risk assessment. Although the majority of immunotoxicity studies are designed for hazard identification, there is a considerable amount of data demonstrating that a threshold for both immunosuppression and contact sensitization exists, making quantitative risk assessment possible. The purpose of this advanced course is to provide guidance on how to perform risk assessment using immunotoxicology data. Following a brief introduction (first presentation), examples will be given for both immunosuppression (second presentation) and contact hypersensitivity (third presentation). In addition, to support animal-to-human extrapolation, mechanistic understanding is crucial and will be provided in this course (last two presentations). In 21st-century toxicology, it also is crucial to integrate all information from in silico and in vitro methods into animal studies. Therefore, in a modern vision of immunotoxicology, integrated strategies will be described and examples provided in each presentation. This course will provide participants with the means and knowledge to conduct quantitative risk assessment using the effect on the immune system as the adverse outcome to protect humans from chemical-induced immunotoxicity and its consequences.

Introduction to the Course. Jamie DeWitt, East Carolina University, Greenville, NC.

Integrated Strategies in Immunotoxicity Risk Assessment. Dori Germolec, NIEHS/NTP, Morrisville, NC.

Quantitative Risk Assessment in Chemical-Induced Skin Sensitization. Frank Gerberick, GF3 Consultancy, LLC, West Chester, OH.

(continued on next page)
Physiologically based pharmacokinetic (PBPK) modeling is widely recognized as a scientifically sound approach to characterize uncertainty in the quantitative relationship between external and internal exposures. The number of regulatory reviews of PBPK models has risen significantly in recent years to support decision-making regarding safety of environmental chemicals and pharmaceutical compounds. For environmental chemicals, PBPK modeling allows for extrapolations across species, life stages, and exposure routes/frequencies, and interpretation of human biomarker measurements. For pharmaceutical compounds, PBPK modeling can be used to identify the need for dose adjustments in subpopulations, the potential for drug-drug interaction, and undesired pharmacokinetics properties such as low bioavailability or rapid clearance. The application of PBPK models to support regulatory risk assessment requires thorough vetting in the context of whether the model’s performance is appropriate for its intended purpose. However, the growing list of applications and different acceptance criteria among agencies and across countries have increased the need for a more standardized approach to both model submission and review processes. To achieve such a goal, this course is designed to provide an overview of how PBPK models might be applied to investigate health outcomes resulting from exposures to environmental or pharmaceutical compounds, as well as to discuss what the key elements being reviewed by different regulatory agencies. This overview will help to promote dialogue among developers, users, and evaluators of PBPK models across government, industry, and academia who seek to establish consistent model submission and review practices. In addition, this course provides training to both modelers and nonmodelers, with the purpose of increasing the pool of potential peer reviewers for regulatory agencies so that they can conduct proper review of models in a timely fashion. To accomplish these training goals, topics to be covered in this course include the principles of pharmacokinetics, fundamental concepts underlying PBPK modeling, data needs, and quality assurance during model development and implementation. The overarching objectives of this course are to highlight opportunities for harmonizing model submission and review processes and to increase the likelihood of model adoption at regulatory agencies. (Disclaimer: the views expressed in this abstract are those of the authors and do not represent Agency policy or endorsement.)


Physiologically Based Pharmacokinetic Modeling and Simulation 101. Andrea Edginton, University of Waterloo, Waterloo, ON, Canada.

Applications of Physiologically Based Pharmacokinetic Models in Clinical Pharmacology. Yuching Yang, US FDA/CDER, Silver Spring, MD.

Physiologically Based Pharmacokinetic Model Construction and Data Needs for Environmental Chemicals. Paul Hinderliter, Syngenta, Greensboro, NC.

Quality Assurance Review of Physiologically Based Pharmacokinetic Models for Regulatory Use. Jordan Smith, Pacific Northwest National Laboratory, Richland, WA.
Every day we use our eyes to see what is going on in the world, while our skin provides key information to our brains by sensing the world around us through touch. Skin also protects our body by regulating our temperature. While the eyes and skin are two distinct organs, they have some commonalities. First, they both provide our bodies with a barrier to the external environment. Although the barrier properties of the skin and cornea are not impermeable or equivalent in their ability to provide protection, they provide a degree of impedance to physical assaults such as sunlight and xenobiotic penetration. Secondly, the outer anatomy of the skin and the eye are epithelial in nature, derived from the ectoderm. These two organs have differences in their physiology, functional purpose, toxicological response, and pathological outcome. Both organs are important to toxicology because they are exposed to the external environment but react differently to toxic insults than internal organs. The purpose of this course is to provide the audience with the fundamentals of dermal and ocular toxicology and methods to assess absorption and toxicity. The first presentation will focus on dermal anatomy and methods to assess dermal absorption. Factors that can affect dermal absorption will be discussed, as well as those learned from in vitro studies (e.g., static, flow-through methods) and in vivo methods to quantitate absorption. The strengths and weaknesses of these methods will be presented. The second presentation will emphasize dermal toxicity. An overview of the manifestations of dermal toxicity, its assessment biomarkers, and useful animal models of chemical-threat agents exposure will be presented. The third presentation will discuss ocular toxicity. The anatomy of the eye and manifestations of ocular injury and toxicity from a variety of drug and chemical classes will be presented. The fourth presentation will highlight toxicology of the cornea. The anatomy of the cornea, absorption of chemicals and drugs through this tissue, and implications of toxicity on the function of the cornea will be presented. The fifth presentation will cover advances in the field of nonanimal alternatives to toxicity testing for skin sensitization and ocular/dermal irritation. Work to develop and validate integrated testing strategies and progress toward regulatory implementation will be discussed. Overall, by attending this session, the audience will gain basic information to understand the potential toxicological outcome of xenobiotic exposure to the dermal and ocular systems.

**Dermal Absorption of Xenobiotics: Skin Anatomy, Factors That Affect Absorption, and Methods to Assess Absorption.** Michael Hughes, US EPA, Research Triangle Park, NC.

**Dermal Toxicity: Hazardous Chemical Exposure Assessment and Animal Models.** Neera Tewari-Singh, University of Colorado Denver, Aurora, CO.

**Ocular Anatomy and Manifestations of Ocular Toxicity.** Marion Gordon, Rutgers, The State University of New Jersey, Piscataway, NJ.

**Tissue-Specific Aspects of Corneal Injury: The Cornea Is Not Merely a Window to the Soul.** Patrick McNutt, US Army Medical Research Institute of Chemical Defense, Fallstom, MD.

**Advances in Nonanimal Alternatives to Dermal and Ocular Toxicity Testing.** Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.
Systematic review is gaining interest in the field of toxicology, highlighted by regulatory requirements being globally instituted to conduct systematic review in support of safety assessments of chemicals and foods (e.g., via US EPA Toxic Substance Control Act (TSCA), US EPA Integrated Risk Information System (IRIS), and European Food Safety Authority (EFSA)). Systematic review refers to the objective and transparent process of collecting and synthesizing scientific evidence for reaching conclusions on specific research questions. While systematic review has been successfully used for decision-making in areas such as clinical medicine for many years, the implementation of systematic review within a toxicological context using established frameworks presents unique challenges. As such, several groups that conduct toxicological research have developed systematic review frameworks that take into consideration the breadth of data relevant to the environmental health and food safety sciences by extending and adapting the approaches developed for clinical medicine. This course will survey available approaches and tools for conducting systematic reviews in toxicology, provide information on the components and conduct of systematic review, and provide instructions on reporting and appraising systematic reviews. Particular emphasis will be placed on determining when a systematic review would be useful and how to determine the specific research question(s), critical appraisal of study quality for human and animal evidence, and structured integration of the evidence across evidence streams. Presenters will highlight and demonstrate tools and other software that can be used for study selection and screening, study quality appraisal, documentation, visualization, and decision-making. The course will provide the opportunity for participants to gain an understanding of why to choose to conduct a systematic review, when it is appropriate to do so, and how to conduct the critical elements of a systematic review, as well as gain an appreciation for the rigor and transparency that a systematic review requires (thus setting it apart from traditional narrative reviews). This course has strong relevance to toxicologists from diverse sectors, including researchers, regulators, risk assessors, consultants, and industry, who may need to use systematic review processes or even consider the results of systematic reviews in their practice.

**Systematic Review: An Overview.** Daniele Wikoff, ToxStrategies, Inc., Asheville, NC.

**Problem Formulation and Protocol Development.** Martin Wilks, University of Basel, Basel, Switzerland.

**Assessment of Study Quality.** Emily Sena, University of Edinburgh, Edinburgh, United Kingdom.

**Integrating the Evidence to Develop Hazard Conclusions.** Brandiese Beverly, NIEHS/NTP, Research Triangle Park, NC.

**Reporting and Critically Appraising Systematic Reviews.** Paul Whaley, Lancaster University and Environment International, Lancaster, United Kingdom.
Current Dose-Response Modeling Strategies and Applications in Chemical Risk Assessment

Sunday, March 10, 1:15 PM to 5:00 PM
PM12 | AFTERNOON COURSE

Chairperson(s): Kan Shao, Indiana University, Bloomington, IN; and Allen Davis, US EPA, Cincinnati, OH.

Primary Endorser: Risk Assessment Specialty Section

Other Endorser(s): Biological Modeling Specialty Section; Regulatory and Safety Evaluation Specialty Section

Quantifying dose-response relationships to evaluate the toxicity of environmental chemicals is a key step in human health risk assessment and has substantially evolved in recent years. The purpose of this course, to be delivered by a mixed group of experts from government, academia, and industry, is to provide participants an overview of the currently prevailing dose-response modeling methodologies and tools with case studies and applications in chemical risk assessment. The first presentation will introduce basic concepts and terminologies of the benchmark dose (BMD) method, including discussions on the use of US EPA benchmark dose software (BMDS), how to model commonly available toxicological data, and how to interpret the results. The second presentation will discuss the categorical regression modeling approach, together with the US EPA Categorical Regression Analysis (CatReg) software and its application to chemical risk assessment. The third speaker will present how to apply the BMD methodology in a Bayesian framework to produce probabilistic estimates of interest (e.g., model parameter estimates, single model BMD estimates, and model averaged BMD estimates) to support probabilistic dose-response assessment. While the first three presentations complement each other regarding modeling methodologies, the last speaker will provide an overview to summarize the utilities of the strategies and tools through three case studies in the agrochemical industry to help participants reinforce the knowledge by using real-world relevance and experience.


Categorical Dose-Response Modeling. Allen Davis, US EPA, Cincinnati, OH.

Bayesian BMD Analysis—Methodologies and Applications. Kan Shao, Indiana University, Bloomington, IN.

Utilization of Dose-Response Modeling Tools for Product Safety Assessment. Zhongyu (June) Yan, Corteva Agriscience, Indianapolis, IN.

Microbiome and Environmental Toxicants: From Study Design and Analysis to Regulatory Guidance

Sunday, March 10, 1:15 PM to 5:00 PM
PM13 | AFTERNOON COURSE

Chairperson(s): Sarah Blossom, University of Arkansas for Medical Sciences, Little Rock, AR; and Sangeeta Khare, US FDA/NCTR, Jefferson, AR.

Primary Endorser: Immunotoxicology Specialty Section

The microbiome consists of indigenous microbial communities and the host environment that they inhabit. Current paradigm-shifting research indicates that the interaction between the host and the microbiome is an important regulator of many diseases and is changing the way that scientists think about the role microbes play in human health. The microbiome includes microbes that are both helpful and potentially harmful, and in a healthy individual, these microbial communities coexist without problems. However, when this balance is disturbed, dysbiosis can occur. One such factor that is emerging as a regulator of this balance is exposure to environmental pollutants that may perturb host-microbiome interactions to promote disease. The microbiome is a rapidly emerging field, and toxicologists from industry, academia, and federal agencies understand the importance of studying the impact of toxicants and pharmaceuticals on gut microbiome dysbiosis and host responses. However, approaching this vast area of study can seem daunting. This course is designed to provide practical information from experts in the field with the latest state-of-the-art tools so that toxicologists can incorporate the study of microbiome and host-associated responses into mechanistic research, risk assessment, and/or therapeutics. Following this course,
participants will be familiar with current advances in microbiome research as it pertains to toxicology. An overview of experimental models and case study examples of microbiome toxicity and immunotoxicity will be presented. Further discussion on how xenobiotics change the microbial population and immune status of animals during developmental exposures will be provided. Concepts will be reinforced in a multigenerational toxicology case study that will take the participants through steps of experimental design, data collection, and reporting. The course will provide participants with practical knowledge and tools to conduct microbiome analysis using the metagenomics analysis server (MG-RAST). The latest information related to regulatory aspects for microbiome-based therapeutics approaches will be presented to participants. Overall, this course will provide a comprehensive overview of study design, data analysis, and challenges in biotherapeutics using examples of toxicant-induced intestinal microbiome dysbiosis.

The Microbiome in Immunotoxicology: Current State-of-the-Science. Sarah Blossom, University of Arkansas for Medical Sciences, Little Rock, AR.


Microbiome Experimental Design for More Effective Planning and Execution of Multigenerational Toxicology Studies. Kenneth Drake, Seralogix, Inc., Austin, TX.

An Overview of Current Microbiome Analysis Tools. Folker Meyer, Argonne National Laboratory and University of Chicago, Argonne, IL.

The Emerging Issue of Microbiome Therapeutics: Regulatory Aspects of Microbiome Perturbation. Paul Carlson, US FDA/CBER, Silver Spring, MD.

Structural and Functional Alterations of Mitochondria in Chemically Induced Cytotoxicity

Sunday, March 10, 1:15 PM to 5:00 PM
PM14 | AFTERNOON COURSE

Chairperson(s): Hilmi Orhan, Ege University, Izmir, Turkey; and Hartmut Jaeschke, University of Kansas Medical Center, Kansas City, KS.

Primary Endorser: Mechanisms Specialty Section

Mitochondria are critical subcellular organelles, as they provide more than 95% of the energy for biochemical and physiological functions, in addition to playing a critical role in lipid metabolism, steroidogenesis, and programmed cell death. In the context of this course, both structural and functional features of the mitochondria will be addressed. Involvement of mitochondria in health and in drug-induced cellular and subcellular toxicities will be discussed, and the practical applications will be described. In the first lecture of this course, the prominent role of mitochondrial toxicity in adverse outcome pathways (AOPs) mechanistically describing a wide spectrum of organ-specific toxicities will be demonstrated. In the second lecture, the central role of mitochondria in drug-induced programmed necrosis and the impact of adaptive mechanisms such as autophagy and mitochondrial biogenesis on cell survival and regeneration will be highlighted. The third lecture will focus on evaluation of mitochondrial function by confocal and multiphoton microscopy, and measurement of respiration and glycolysis. In the last lecture, the metabolic capacity of mitochondria in terms of local reactive metabolite generation, as well as toxicological outcomes, will be discussed.

Mitochondrial Toxicity: A Frequent Key Event in Adverse Outcome Pathways. Mathieu Vinken, Vrije Universiteit, Brussels, Belgium.

Mitochondria as Critical Regulators of Drug-Induced Organ Toxicity and Recovery. Hartmut Jaeschke, University of Kansas Medical Center, Kansas City, KS.

Assessment of Mitochondrial Dysfunction in Drug- and Oxidant-Induced Cytotoxicity. John Lemasters, Medical University of South Carolina, Charleston, SC.

Local Bioactivation of Drugs and Other Chemicals in Mitochondria: Toxicological Outcomes. Hilmi Orhan, Ege University, Izmir, Turkey.
Scientific Sessions

Featured Sessions

Opening Plenary Lecture: Robust Assembly of Human Tissues for Disease Modeling and Discovery

Monday, March 11, 8:00 AM to 9:00 AM

Lecturer: William L. Murphy, University of Wisconsin-Madison, Madison, WI.

The need for human, organotypic culture models coupled with the requirements of contemporary drug discovery and toxin screening (i.e., reproducibility, high throughput, transferability of data, clear mechanisms of action) frame an opportunity for a paradigm shift. The next generation of high-throughput cell-based assay formats will require a broadly applicable set of tools for human tissue assembly and analysis. Toward that end, we have recently focused on (1) generating iPS-derived cells that properly represent the diverse phenotypic characteristics of developing or mature human somatic cells, (2) assembling organotypic cell culture systems that are robust and reproducible, (3) translating organotypic cell culture models to microscale systems for high-throughput screening, and (4) combining genomic analyses with bioinformatics to gain insights into organotypic model assembly and the pathways influenced by drugs and toxins. This lecture will emphasize recent studies in which we have explored assembly of organotypic vascular, liver, and brain tissues. These tissues mimic critical aspects of human organ structure and can be used for reproducible identification of drug candidates and toxic compounds. Our work particularly emphasizes reproducibility and data transferability, which we view as vital to the widespread use of organotypic human models in toxicity testing. The lecture will also introduce the use of our assembled human tissues to develop models of rare developmental disorders and degenerative diseases of the brain.

Keynote Medical Research Council (MRC) Lecture: Ageing and Multimorbidity: Time for a New Approach

Wednesday, March 13, 12:30 PM to 1:30 PM

Lecturer: Janet M. Lord, University of Birmingham Institute of Inflammation and Ageing, Birmingham, United Kingdom.

The lecture will review current demographic trends and also describe data for the incidence of multimorbidity in older adults. Dr. Lord’s recent analysis of patients admitted to the Queen Elizabeth Hospital Birmingham, United Kingdom, in 2016 revealed that 75% of the emergency admissions were for those aged over 50 and of those patients 83% had three or more diseases and 70% had four or more. Age is the biggest single risk factor for multimorbidity, yet we continue to treat the composite diseases individually, resulting in polypharmacy. A case will be made for targeting core ageing processes as a way to make clinical impact in multimorbid patients. The lecture will
describe recent advances in biogerontology that have revealed the core processes that drive the ageing process, including cell senescence, reduced DNA damage repair, and loss of proteostasis, and review interventions in these processes in mice that have extended life span and health span.

The second half of the lecture will cover work on the contribution made to the ageing phenotype of a decline in immune function. This work has shown that reduced neutrophil function contributes to increased susceptibility to infection as well as the frailty associated with infections in the elderly. The lecture will describe recent work showing that neutrophil migratory defects are driven by constitutive signaling through PI3 kinase delta and can be reversed either by inhibition of this pathway by selective PI3k inhibition, or by targeting downstream GTPases through statins. Data will be presented on the reversal of neutrophil ageing by statins in vitro and in vivo and report on a clinical trial with statins that showed improved recovery from pneumonia in older patients. The lecture will conclude with a presentation of unpublished data on the role played by NK cells in the accumulation of senescent cells with age, one of the core ageing drivers.

SOT/EUROTOX Debate: Classification of Substances as Endocrine Disruptors Has a Public Health Benefit

Monday, March 11, 4:45 PM to 6:00 PM

Chairperson(s): George Daston, Procter & Gamble Company, Cincinnati, OH; and Félix Carvalho, University of Porto, Porto, Portugal.

SOT Debater: Paul Foster, NIEHS (Retired), Research Triangle Park, NC.

EUROTOX Debater: Martin van den Berg, Utrecht University, Utrecht, Netherlands.

Each year, the SOT Annual Meeting includes a debate in which leading toxicologists advocate opposing sides of an issue of significant toxicological importance. The debate continues a tradition that originated in the early 1990s. This year, the debaters will address the proposition “Classification of Substances as Endocrine Disruptors Has a Public Health Benefit.”

Endocrine disruptors are compounds that produce adverse responses in various organ systems, but particularly the reproductive system, by interfering with normal hormonal signaling. There has been considerable public concern about endocrine disruptors, particularly in how much of a role they may play in causing certain cancers, infertility, and birth defects, as well as population declines in wildlife. This public concern has led to the passage of various laws in the United States and Europe to identify and regulate compounds that have endocrine-active properties. This includes action by the European Commission to develop a classification system for endocrine disruptors. It is unclear, however, whether classification as an endocrine disruptor conveys any public health benefit; endocrine disruption is a collection of modes of action, not an adverse response, and if the adverse responses are already the subject of regulation, does classification provide any additional protection? The debaters will discuss whether there is value in an additional classification scheme.

In addition to the inclusion as a Featured Session at this meeting, this debate will again take place (with the debaters taking the reverse positions) in Helsinki, Finland, during the 55th Congress of the European Societies of Toxicology (2019 EUROTOX Annual Congress), September 8–11, 2019.
Society of Toxicology and Japanese Society of Toxicology Symposium:
Epigenetic Modifications in Chronic Pathology and Toxicology

Tuesday, March 12, 8:00 AM to 10:45 AM

Chairperson(s): Ron Hines, US EPA, Research Triangle Park, NC; and Akihiko Hirose, National Institute of Health Sciences Japan, Kawasaki, Japan.

SOT and the Japanese Society of Toxicology are delighted to jointly sponsor a symposium on a topic of mutual interest: epigenetic modifications in chronic pathology and toxicology. Each society has selected from among its membership true leaders in the field to provide their perspectives on recent advances in this area. The epigenome functions to regulate gene expression through chemical modifications to DNA and its histone protein scaffolding, as well as through the differential expression of non-coding RNAs. In contrast to DNA, where preservation of DNA fidelity is of utmost importance, the epigenome exhibits tremendous plasticity, and can respond to a range of environmental factors, including chemical exposures, diet, and stress. Consequently, epigenetic mechanisms are now well recognized as having an important role in determining toxicant-dependent adverse health outcomes. Within an adverse outcome pathway framework, toxicant-induced changes in the epigenome can alter the dose-response relationship at one or more key elements and thus impact susceptibility. More direct impacts on key elements can occur through toxicant-induced changes in the epigenome that manifest in acute gene expression changes or can persist but remain silent until activated by a second signal and then drive inappropriate gene expression at a critical window of time. This symposium will explore different avenues of research that are improving our understanding of toxicant-induced changes in the epigenome and our ability to predict adverse outcomes, but also how we are taking advantage of chemical-dependent epigenome changes to open up a new chemical space for therapeutics.

Development of Small Molecules Targeting Transcription and Splicing Machinery against Viral Infections and Genetic Diseases: Their Potential Risks and Merits. Masatoshi Hagiwara, Kyoto University, Kyoto, Japan.

Epigenetic Mechanism of Modification of a Gene Expression Network Induced by a Repeated Exposure to a Chemical. Jun Kanno, Japan Bioassay Research Center, Kanagawa, Japan.

Epigenetics and the Use of piRNA for Epigenome Editing in Environmental Health Research. Dana C. Dolinoy, University of Michigan School of Public Health, Ann Arbor, MI.

Developmental Reprogramming of the Epigenome by Early-Life Environmental Exposures. Cheryl Lyn Walker, Baylor College of Medicine, Center for Precision Environmental Health, Houston, TX.

Find up-to-date information at www.toxicology.org/2019 | #2019SOT #toxexpo
Meet the Directors: A Conversation with Linda S. Birnbaum, Jennifer Orme-Zavaleta, and Mark S. Johnson

Tuesday, March 12, 11:00 AM to 12:00 Noon

Chairperson(s): Ron Hines, US EPA, Research Triangle Park, NC.


This important session will provide an informal venue for meeting attendees to have a candid and open discussion with three key leaders of federal organizations with missions to protect and improve public health and the environment: Linda S. Birnbaum, PhD, Director, National Institute of Environmental Health Sciences (NIEHS); Jennifer Orme-Zavaleta, PhD, Principal Deputy Assistant Administrator for Science, US EPA Office of Research and Development, and Agency Science Advisor; and Mark S. Johnson, PhD, DABT, ATS, US Department of Defense (US DoD). The entire session will be devoted to a question-and-answer format concerning scientific directions and priorities for NIEHS, US EPA, and US DoD (e.g., DTRA, DARPA, SERDP, and ESTCP), including funding priorities and outlooks and training opportunities. Dr. Birnbaum has served as the director of NIEHS and the National Toxicology Program since 2009. Dr. Orme-Zavaleta has been with the US EPA since 1981, working in the areas of human health and ecological research, risk assessment, policy and regulation development, strategic planning, and program implementation. Before assuming her current position in 2017, she served as the director of the US EPA National Exposure Research Laboratory and as the interim national program director for Safe and Sustainable Water Resources. Dr. Johnson is the director of toxicology at the Army Public Health Center and the chair of the Tri-Service Toxicology Consortium.

Toxicological Sciences Featured Session: From the Pages of ToxSci: Mouse vs. Machine ... Are Animal Studies Being Supplanted by Computers?

Tuesday, March 12, 1:00 PM to 2:30 PM

Chairperson(s): Gary W. Miller, Columbia University, New York, NY; ToxSci Editor in Chief.

Panelists: Gary W. Miller, Columbia University, New York, NY; Alison Harrill, NIEHS/NTP, Research Triangle Park, NC; Thomas Hartung, Johns Hopkins University Center for Alternatives to Animal Testing (CAAT), Baltimore, MD; Nicole C. Kleinstreuer, NIEHS, Research Triangle Park, NC; and Ivan Rusyn, Texas A&M University, College Station, TX.

Computational approaches for predicting toxicological outcomes have dramatically improved over the past few years. Many of these advances have been reported in Toxicological Sciences. This session will feature a panel of experts to discuss, debate, and examine the current state of the art in computational toxicology. The panel will explore the possibility of a future without animal testing in toxicology. Each panelist will be given five minutes to provide context for the discussion. Attendees will be encouraged to contribute to the discussion via a moderated Q&A.
EUROTOX Bo Holmstedt Memorial Lecture: Metabolism, Inflammation, and Cancer

Wednesday, March 13, 11:00 AM to 12:00 Noon

Lecturer: Nigel J. Gooderham, Imperial College London, London, United Kingdom.

Born in the southern part of Sweden in 1918, Professor Bo Holmstedt was an internationally renowned toxicologist. He was known for his outstanding research contributions and his engagement in education and was a leading figure in the toxicology community. In his memory, EUROTOX established the Bo Holmstedt Memorial Lecture. This merit award recognizes excellence in toxicological sciences and is presented to an outstanding European toxicologist at the EUROTOX Annual Congress. The SOT Scientific Program Committee is pleased to present a lecture exchange of eminent scientists between SOT and EUROTOX. As part of the exchange, Dr. Nigel Gooderham (2018 Bo Holmstedt Memorial Lecture awardee) will present at the SOT Annual Meeting, and an SOT Merit Award recipient will present at the 2019 EUROTOX Annual Congress in Helsinki, Finland, in September.

Publication of Detoxication Mechanisms (R. Tecwyn Williams, 1947) established the discipline of drug metabolism as a pillar of toxicology and chemical carcinogenesis. In exploring this role of metabolism in carcinogenesis, we and others studied the metabolism of food-derived heterocyclic amines (HA) and their potential role in diet-associated human cancer. It was established that HAs are metabolically activated via amine oxidation, catalysed by CYP1 enzymes then esterification. The food-derived HA, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), determined to be genotoxic and potently estrogenic, emerged as a strong candidate for involvement in diet-associated cancer. The hypothesis that HAs contributed to colorectal cancer was examined in a case-control study. The data failed to support the hypothesis but characterized the inflammation phenotype of colorectal tumor tissue (COX2, IL-1b, IL-6, NF-kB, and IKK-a). An inflammation-cancer association was first reported more than a century ago, and inflammation was shown to reduce CYP-mediated metabolism 40 years ago. Yet in our clinical samples, although tumor CYP expression differed from that of adjacent normal tissue, there was selective induction of CYP1B1 and 2E1. Turning to mechanistic studies, we confirmed that IL6 treatment induced CYP1B1 and CYP2E1, and that IL6-mediated CYP2E1 regulation occurred via STAT3 and CYP1B1 elevation via downregulation of microRNA miR27b. Thus, inflammation at colonic neoplastic tissue alters metabolic competency by manipulating CYP2E1 and CYP1B1 expression through transcriptional and epigenetic mechanisms. We hypothesized that this could increase metabolic activation and DNA damage and showed that the dietary carcinogens benzo[a]pyrene (BaP) and PhIP induced genotoxicity that was enhanced by IL6. Tumors are infiltrated by stromal cell types that interact with malignant cells. This microenvironment is thought to be regulated by the tumor to promote survival and progression. We showed that IL6 secreted by immune cells not only increases selective metabolic competency but also promotes colorectal cancer cell invasiveness and secretion of microRNAs such as miR21 and miR29b. In turn, these microRNAs induce immune cell IL6 production and release miR21 into the microenvironment. Thus, cancer and immune cells communicate via IL6 and miRNAs to sustain chronic inflammation, promote selective metabolic competency and pro-metastatic cancer cell behavior. These findings identify key players that metabolically empower colon cancer cells and mediate intercellular communication and offer therapeutic opportunities to target the cancer microenvironment.
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July 15–18, 2019
Symposium Sessions | Monday

**Advances in In Vitro to In Vivo Extrapolation: Approaches and Applications**

**Monday, March 11, 9:15 AM to 12:00 Noon**

*Chairperson(s):* Ben van Ravenzwaay, BASF SE, Ludwigshafen, Germany, and Wageningen University, Wageningen Netherlands; and Barbara Wetmore, US EPA, Research Triangle Park, NC.

**Primary Endorser:** Biological Modeling Specialty Section

**Other Endorser(s):** Computational Toxicology Specialty Section; *In Vitro* and Alternative Methods Specialty Section

The development of nonanimal-based testing strategies of chemicals is important in current human safety testing. Many efforts focus on the development and standardization of *in vitro* new approach methodologies (NAMs) that provide concentration-response data. However, concentration-response data obtained from *in vitro* models are inadequate for human risk and safety assessment. In order to use these data for risk assessment purposes, the *in vitro* concentration-response data should be translated to *in vivo* dose-response data to obtain points of departure to set safe human exposure levels. It has been proven that *in vivo* dose-response data can be predicted by *in vitro* concentration-response data using physiologically based kinetic (PBK) modeling-based reverse dosimetry, thus enabling the use of *in vitro* toxicity data for risk assessment and prioritization. In the PBK modeling-based reverse dosimetry approach, the *in vitro* effect concentrations are set as equal to the blood or tissue effect concentrations, following which the PBK model can calculate the corresponding *in vivo* dose levels that are required to reach the same level of blood or tissue concentrations. Current research focuses on the development of *in vitro* assays and QSAR models for obtaining parameter values needed for the PBK models, as well as the use of PBK modeling-based reverse dosimetry to predict toxic dose levels based on *in vitro* toxicity data. The first talk will provide an overview of PBK modeling-based *in vitro* to *in vivo* extrapolation (IVIVE), including the concept of the approach and the application of the developed approach for the prediction of toxic dose levels based on *in vitro* data. The second talk will discuss the *in vitro* models and QSAR models developed to obtain the input parameter values for the development of the PBK model. The third talk will focus on the evaluation and application of IVIVE for risk assessment purposes using high-quality data and open-source, user-friendly tools. The fourth presentation will describe the development and evaluation of a generic PBK model for a series of compounds tested in assays for estrogenic activity. The fifth talk will provide a case study for antiandrogens and give an outlook of industry use of the PBK modeling-based IVIVE for toxicological assessment of chemicals. This session will bring together academic, government, and industry scientists to give an overview of the IVIVE approach. Relevant to the field of toxicology, the application of *in vitro* NAMs and QSAR models developed for PBK models, the evaluation of the extrapolation approach, and how to apply this concept in risk assessment and chemical prioritization will be discussed in this symposium and in a concluding Q&A session with the audience.

**Introduction.** Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.

**Advances in In Vitro-In Vivo Extrapolation (IVIVE) Tools for Chemical Toxicokinetics: Refinements and Considerations for International Adoption and Use.** Barbara Wetmore, US EPA, Research Triangle Park, NC.

**Quantitative In Vitro-In Vivo Extrapolation (QIVIVE), Models, and Input Parameters.** Nynke Kramer, Utrecht University, Utrecht, Netherlands.

**IVIVE Tools for Risk Assessment.** Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.

**PBK Modeling-Based IVIVE for the Toxicological Assessment of Potential Endocrine Disruptors.** Eric Fabian, BASF SE, Ludwigshafen, Germany.

**Development of a Generic Physiologically Based Kinetic Model to Predict In Vivo Endocrine Activity in Rats Based on In Vitro Bioassays.** Mengying Zhang, Wageningen University, Wageningen, Netherlands.

**Panel Discussion/Q&A.**
Alpha-Synuclein: A Good Protein Turned Bad in Chronic Brain Diseases with Toxicological Implications

Monday, March 11, 9:15 AM to 12:00 Noon

Chairperson(s): Wei Zheng, Purdue University, West Lafayette, IN; and Anumantha Kanthasamy, Iowa State University, Ames, IA.

Primary Endorser: Neurotoxicology Specialty Section

Other Endorser(s): Mechanisms Specialty Section; Metals Specialty Section

Alpha-Synuclein (aSyn) is a low molecular weight (14.5 kDa), natively unfolded protein expressed in a wide range of cell types and is particularly abundant in presynaptic terminals. The exact function of aSyn remains uncertain; however, recent evidence suggests that aSyn functions in the brain to maintain synaptic plasticity, regulate dopamine synthesis, and facilitate vesicular dynamics, (e.g., stabilization and exocytic fusion at presynapses). Dysfunction and aggregation of aSyn has been associated with the pathoetiology of Parkinson's disease (PD), Alzheimer's disease (AD), and Diffused Lewy Body disease (DLB). The monomeric form of aSyn in the brain mainly originates from neuronal cells, yet aSyn present in the circulatory system can pass across the blood-brain barrier (BBB) to enter the brain parenchyma. Recent studies have explored the possibility of using total plasma levels of aSyn as a surrogate marker for the progression of PD and other neurodegenerative diseases such as AD. Thus, it is imperative to understand the mechanism by which the BBB regulates the fluxes of aSyn in and out of the brain to maintain aSyn homeostasis in the central milieu. Excessive aSyn proteins in brain tend to misfold, leading to massive aggregation in Lewy bodies. This aggregation is believed to be promoted by the binding of the protein to phospholipid membranes and by post-translational modifications resulting from mitochondrial dysfunction/oxidative stress. aSyn has divalent metal binding sites that are known to affect the protein stability. Toxicological findings support a role for aSyn in chemically induced Parkinsonian disorders; for example, exposure to beta-carboline derivatives in food and manganese in the environment greatly increases aSyn aggregation. Also, certain pesticides are known to upregulate aSyn expression. These discoveries have established causal relationships between the environmental exposure to toxic substances and altered aSyn gene expression, increased influx to brain, decreased clearance from brain parenchyma, and ultimately accelerated aSyn aggregation. This session brings together in one place the worldwide experts who are actively investigating aSyn biology, chemistry, neurotoxicity, its underlying cellular and molecular mechanisms, and clinical consequences, to address an interesting question: How does a “good” aSyn protein change to be a culprit in environmentally linked neurodegenerative diseases. After a brief introduction of aSyn in health and human diseases, the first presenter will highlight the current understanding of mechanisms of aSyn self-assembly and how exposure to environmental toxicants promotes the protein’s aggregation. The second presenter will discuss the potential of using total plasma levels of phosphorylated aSyn in the cerebrospinal fluid (CSF) and plasma to diagnose AD and PD, based on human longitudinal studies, and how this approach may be applied to neurotoxicological investigations. The third presenter will extend the subject to illustrate the processes that regulate aSyn transport by the BBB and how the altered aSyn transport at brain barriers may lead to Parkinsonian disorders. The last presenter will report the latest findings showing that Mn exposure enhances the release of misfolded aSyn via exosomes by impairing endosomal trafficking machinery. A sensitive high-throughput method to quantify aSyn in welder’s serum will also be introduced. This session will present the latest discoveries on the structural, genetic, cellular, and molecular mechanisms of aSyn in neurodegenerative diseases. The session will capture a broad interest from those engaged in toxicological research of neurodevelopment and neurodegenerative diseases, neuroscience, neurotoxicology, metal toxicology, and nanoscience.

Alpha-Synuclein in Health and Diseases: An Introduction. Wei Zheng, Purdue University, West Lafayette, IN.

How aSyn Converts from Good to Bad: A Role for Environmental Toxicants. Jean-Christophe Rochet, Purdue University, West Lafayette, IN.

Potential Roles of Peripheral aSyn in Alzheimer’s and Parkinson’s Diseases: Implication in Toxicological Studies. Jing Zhang, University of Washington, Seattle, WA.

Transport of aSyn by Brain Barrier Systems and Relevance to aSyn Toxicity. Anne Mahringer, University of Heidelberg, Heidelberg, Germany.

Translational Relevance of Misfolded aSyn Release via Exosomes in Manganese-Induced Parkinsonian Disorder. Anumantha Kanthasamy, Iowa State University, Ames, IA.

Panel Discussion/Q&A.
Assessing Acute Health Risk: Potential Application of Next-Generation Toxicological Tools

Monday, March 11, 9:15 AM to 12:00 Noon

Chairperson(s): Michael Stewart, US EPA, Research Triangle Park, NC; and Brian Chorley, US EPA, Research Triangle Park, NC.

Primary Endorser: Risk Assessment Specialty Section

Other Endorser(s): Exposure Specialty Section; Molecular and Systems Biology Specialty Section

Human health risk assessments estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in the environment. Estimates of health risks resulting from chemical exposure are typically based on an assumption that either low-level, chronic (~year or more) or higher-level, acute (~day or less) exposures adequately span the range of all other potential scenarios. However, there are relatively few health effect toxicity values applicable to the general population for acute exposures as opposed to chronic chemical exposures. A primary reason is that a large number of chemicals have a paucity of short-term human and animal data on which to base acute toxicity values. In vitro, computational modeling, conceptual frameworks, and other higher-throughput measurements may help fill these gaps. These next-generation tools have been slowly integrated into chronic chemical hazard prioritization over the last decade, but the use of these tools to quantitatively derive reference values for acute exposure scenarios has not been widely discussed even though these studies are inherently acute in nature. This session will first explore how acute toxicity values are currently being derived and used to assess the potential for short-term risk. The session will continue to discuss both the challenges and the promises of using next-generation toxicological tools (specifically pharmacokinetic or pharmacodynamic modeling, adverse outcome pathway frameworks, and high-throughput testing strategies) to address data deficiencies associated with the derivation and proper application of acute health toxicity values.


Exposure Assessment and Risk Management Using Acute Toxicity Factors to Evaluate Ambient Air Monitoring Data in Texas. Tiffany Bredfeldt, Texas Commission on Environmental Quality, Austin, TX.

A Conceptual Model for Predicting How Acutely Toxic Exposure Levels Should Relate to Those Associated with Toxicity from Longer-Term Exposures, Suggesting Approaches to Using In Vitro Data in Exposure-Duration Extrapolation. Lorenz Rhomberg, Gradient, Cambridge, MA.

Application of Modern Toxicology Approaches for Predicting Acute Toxicity. David Dorman, North Carolina State University, Raleigh, NC.

Predicting Chemical Affinity and Extrapolating to Safe Acute Exposure Levels (SAELs). Lyle Burgoon, US Army Engineer Research and Development Center, Vicksburg, MS.


Panel Discussion/Q&A.
The genetic information encoded in DNA and perturbations in the flow of genetic information from DNA to downstream biomolecules (i.e., RNA then protein) following chemical exposure are critical determinants of toxicological responses in terms of both functional outcomes and variations in response across a population (i.e., inter-individual susceptibility). In general, toxicologists have been cautious regarding when and how to incorporate information about genetically controlled responses or genetic susceptibility into safety and risk assessment pipelines. However, there are a number of recently developed molecular biology tools that can be used to evaluate the role of genetic structure, gene regulation, and gene expression in response to drug and chemical exposures that provide informative data for use in various steps across risk evaluation pipelines. The aim of this session is to discuss emerging systems genetics tools that may help advance toxicological evaluation and to present case studies demonstrating their utility. Tools and approaches that will be discussed in this session include (1) the use of genetically diverse population models for investigating the contribution of genetic sequence variation to toxicant susceptibility and applications toward replacement of default toxicodynamic uncertainty factors, (2) the use of gene-editing technologies in a screening context toward discovery of key genetic drivers underlying susceptibility and resistance to toxicant exposures, (3) the use of methylome-based next-generation sequencing (NGS) for rapid assessment of toxicant-induced changes in DNA methylation patterns and applications for adverse outcome pathway (AOP) integration, (4) the use of targeted RNA-seq in a high-throughput transcriptomics (HTTr) screening context and methods for in vitro point-of-departure estimation and in vitro to in vivo extrapolation (IVIVE), and (5) the use of weighted gene co-expression networks (WGCNA) for toxicant mode-of-action analysis. Participants in the session will gain a broader understanding of emerging genetic and transcriptomic analysis tools, their strengths and limitations, and their applications in testing prioritization, mechanistic analysis, and human health risk assessment.

**Introduction.** Joshua Harrill, US EPA, Research Triangle Park, NC.

**Quantifying Inter-Individual Toxicodynamic Variability Using Genetic Reference Populations to Inform Risk Assessment.** Alison Harrill, NIEHS/NTP, Research Triangle Park, NC.

**Genome-Wide and Targeted CRISPR Functional Approaches in Toxicology.** Chris Vulpe, University of Florida, Gainesville, FL.

**Novel Methods for Rapid Assessment of Toxicant-Induced Changes in DNA Methylation.** Brian Cummings, University of Georgia, Athens, GA.

**High-Throughput Transcriptomics (HTTr) Screening with Targeted RNA-Seq: Applications for In Vitro Point-of-Departure Estimation and In Vitro to In Vivo Extrapolation.** Joshua Harrill, US EPA, Research Triangle Park, NC.

**TXG-Map: Systems Biology Approaches to Understanding Adverse Outcomes.** Yue Webster, Eli Lilly and Company, Indianapolis, IN.

**Panel Discussion/Q&A.**
Application of Computational Modeling to Risk Assessment of Endocrine Disruptors

Monday, March 11, 9:15 AM to 12:00 Noon

**Chairperson(s):** Qiang Zhang, Emory University, Atlanta, GA; and Hisham El-Masri, US EPA, Research Triangle Park, NC.

**Primary Endorser:** Biological Modeling Specialty Section

**Other Endorser(s):** Computational Toxicology Specialty Section

Endocrine disruption is a major health concern for many persistent environmental chemicals, with adverse outcomes in metabolism, development, reproduction, and cancer. The endocrine systems are robust nonlinear dynamical systems by nature, which can resist perturbations to maintain hormone homeostasis through feedback regulations between multiple organs. Simple, linear extrapolation from high-dose data to environmental low-dose effects is thus not applicable to predicting the health risk of endocrine-disrupting chemicals (EDCs). Moreover, as toxicity testing is increasingly shifting to cell- or organoid-based *in vitro* assays, the demand for *in vivo* extrapolation that can predict systems-level hormonal outcomes and apical endpoint consequences in human populations is also rising. Bridging these data gaps calls for a computational systems biology approach to mechanistically model the endocrine systems and their responses to perturbations by endocrine disruptors acting via diverse molecular initiating events (MIEs). This session is organized to present the state-of-the-science in mathematical modeling of endocrine systems in the context of chemical risk assessment through presentations of a series of computational works on thyroid, reproductive, and adrenal systems. The first presenter lays out the general design principles for the homeostatic regulation of the endocrine systems involving feedback interactions between the hypothalamus, pituitary, and endocrine organs. Using the thyroid system as an example, the presentation illustrates how mechanistic computational models constructed according to these principles and incorporating individual variability can aid the interpretation and quantitative prediction of the health outcomes of EDCs. The second talk presents a more detailed model of the thyroid system to understand the effect of iodine nutritional status on thyroid hormone levels during pregnancy and lactation. While the model is unable to explain why repletion of iodine intake cannot ameliorate the effect of iodine deficiency, it provides mechanistic insights into the dynamic functioning of the hypothalamic-pituitary-thyroid (HPT) axis during the reproductive stage of women. The third talk presents the modeling work on *in vitro* to *in vivo* extrapolation (IVIVE) for the risk effects of EDCs in both the thyroid and male reproduction systems. By using *in vitro* data from thyroxine oxidase and sodium-iodide symporter inhibition assays and a purified rat Leydig cells assay that detects alterations in testosterone production, the speaker illustrates quantitative adverse outcome pathway (qAOP) models that can extrapolate these *in vitro* data to predict mammalian neurodevelopmental deficits. The fourth talk presents the modeling work on the hypothalamic-pituitary-adrenal axis and how its interaction with the circadian rhythm can affect between-sex and within-sex variability. The model provides a computational tool that can be tapped to understand the heterogeneous responses in human populations to stress and to aid risk assessment of EDCs interfering with the physiological stress response. The final presentation includes a comprehensive modeling framework that links exposure, toxokinetic, and ovarian cycle models. The work illustrates how modeling the exposure-to-outcome continuum through linking these models and incorporating ToxCast assay data can predict the mixture effects of aromatase inhibitors on menstrual cycle length and ovulation. In summary, the session will demonstrate that through integrating chemical and biological data from *in vitro*, *in vivo*, epidemiology, and exposure studies, computational systems biology models of endocrine systems can play a key, bridging role in quantitatively understanding and predicting the health risks of EDCs.

**Introduction.** Qiang Zhang, Emory University, Atlanta, GA.

**Design Principles of Endocrine Systems and Their Applications to Understanding Endocrine Disruptions: A Case Study with the Hypothalamic-Pituitary-Thyroid Axis.** Qiang Zhang, Emory University, Atlanta, GA.

**Using Computational Approaches to Understand the Hypothalamic-Pituitary-Thyroid (HPT) Axis for Iodine Sufficient and Insufficient Conditions during Lactation.** Jeff Fisher, US FDA/NCTR, Jefferson, AR.

(continued on next page)

Personalized Adaptation to Stress and Physiological Trade-Offs in the Circadian Regulation of the HPA Axis: A Systems Biology Approach. Ioannis Androulakis, Rutgers, The State University of New Jersey, Piscataway, NJ.


**Panel Discussion/Q&A.**

### MALDI Tissue Imaging: A New Tool for Making TK/TD Connections to Histopathology

**Monday, March 11, 9:15 AM to 12:00 Noon**

**Chairperson(s):** Laura Schnackenberg, US FDA/NCTR, Jefferson, AR; and Lisa Cazares, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD.

**Primary Endorser: Toxicologic and Exploratory Pathology Specialty Section**

Matrix-assisted laser desorption/ionization imaging mass spectrometry, or MALDI IMS, is an emerging label-free technology, which can provide the spatial distribution of drugs, drug metabolites, lipids, and other endogenous analytes in tissue samples. The analyte tissue distributions, when correlated with histopathology, provide detail that may allow a better understanding of a drug’s mechanism of action or the effects of a toxicological insult. MALDI IMS provides high spatial resolution (10 µm), is highly sensitive, and can be quantitative, qualities that have propelled the use of MALDI IMS across a variety of disciplines, including toxicological applications. This session will explore the recent incorporation of MALDI IMS to inform TK/TD drug decisions, a tool for identifying biomarkers related to histopathology and toxicity, and a method for identifying n-linked glycans across a variety of diseases and therapeutic models. Presenters representing government, academia, and pharmaceutical sectors will share recent MALDI IMS data from toxicology studies. The first presentation will provide a brief overview of MALDI IMS, including its strengths and limitations as a new tool for toxicology. The second presenter will discuss the role of MALDI-FTICR imaging to assist the United States Department of Defense at Fort Detrick to evaluate changes in metabolites in relation to infection from viral or bacterial pathogens. The third presenter will discuss the recent incorporation of MALDI IMS to assess drug, metabolites, and histopathological changes in a zebrafish model of drug-induced kidney toxicity. The fourth presentation will present case studies in drug development whereby MALDI IMS was utilized to better understand PK/PD relationships within a drug development pipeline. Finally, a cutting-edge and recent application of MALDI IMS will be presented, whereby n-linked glycan distributions can be identified in formalin-fixed paraffin-embedded (FFPE) tissues and microarrays from cancer biopsies. Use of this approach to further understand how glycan profiles and glycoproteins respond to therapeutics or xenobiotic exposures also will be discussed.

**MALDI IMS: An Emerging Technology in the Field of Toxicology.** Laura Schnackenberg, US FDA/NCTR, Jefferson, AR.

**MALDI-FTICR Mass Spectrometry Imaging Reveals Dysregulated Lipid and Small Molecule Metabolites in Tissues Harvested from Mice Infected with a Bacterial or Viral Pathogen.** Lisa Cazares, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD.

**Matrix Assisted Laser Desorption Ionization Imaging Mass Spectrometry (MALDI IMS) of Drug-Induced Toxicity in a Zebrafish Model.** E. Ellen Jones, US FDA/NCTR, Jefferson, AR.

**MALDI IMS: Visualizing Pharmacologically Active Molecules “Breaking Bad” in Tissue.** Steve Castellino, GlaxoSmithKline, plc, King of Prussia, PA.

**Mapping Changes in Tissue N-Linked Glycosylation Patterns in Carcinogenesis, Knockout, and Treatment/Drug Resistance Models.** Richard Drake, Medical University of South Carolina, Charleston, SC.

**Panel Discussion/Q&A.**
Complications arising from diabetes mellitus (DM) is the seventh leading cause of death in the US. Approximately 30.3 and 84.1 million Americans had type II DM or prediabetes, respectively, in 2015. The number of Americans with type II DM is projected to increase by nearly 20 million from 2015 to 2030. Lifestyle choices such as diet and exercise, in addition to genetics, are major factors in determining if someone will become type II DM. In addition to these factors, exposure to environmental metal and nonmetal substances (e.g., cadmium, arsenic, zinc, manganese, and selenium) may also play a significant role. Many epidemiological studies show a significant and positive association between exposure to toxic environmental metals and type II DM, prediabetes, or impaired fasting glucose. Experimental studies using animal models of metal toxicity show significant increases in fasting blood glucose levels or disruption of major mediators of metabolism. This session will examine the cellular and molecular mechanisms responsible for the diabetogenic effects of various metals. In addition, factors that may mitigate arsenic-induced dysglycemia, such as selenoproteins, will be discussed. Lastly, the session will review the synergistic or additive effects of cadmium-induced nephrotoxicity in an in vitro model of diabetic nephropathy. This session will highlight the most recent experimental findings from presenters who are experts at the forefront of this field of study.

Cadmium Accumulates within Pancreatic Islets at Levels Similar to the Renal Cortex in an Experimental Model of Long-Term Exposure. Joshua Edwards, Midwestern University, Downers Grove, IL.

Methods of Investigating the Toxic Potential of Environmental Factors in Insulin-Producing Islets of Langerhans Illustrated Using the Example of Cadmium. Malek El Muayed, Northwestern University, Chicago, IL.

Dissecting Mechanisms of Metal-Induced Beta Cell Dysfunction: Arsenic, Cadmium, Manganese, and Zinc. Mirek Styblo, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Selenium and Selenoproteins Modulate Arsenic-Induced Metabolic Dysfunction. Robert Sargis, University of Illinois at Chicago, Chicago, IL.

Hyperglycemic Glucose and Cadmium Exposure: Two Loads Too Many for the Renal Proximal Tubule. Scott Garrett, University of North Dakota, Fargo, ND.

Panel Discussion/Q&A.
Pharmaceutical Investigative Toxicology: Case Studies in Optimizing Drug Discovery and Guiding Human Risk Assessment

Monday, March 11, 9:15 AM to 12:00 Noon

Chairperson(s): Clay Scott, AstraZeneca, Waltham, MA; and Howard Mellor, Vertex Pharmaceuticals, Oxford, United Kingdom.

Primary Endorser: Drug Discovery Toxicology Specialty Section

Other Endorser(s): Mechanisms Specialty Section

Toxicity and clinical safety have a major impact on drug development success. Moving toxicological studies into earlier phases of the research and development chain prevents drug candidates with a safety risk from entering clinical development. However, to identify candidates without such risk, safety has to be addressed proactively. Therefore, toxicology should ideally be integrated into the discovery process. Successful discovery phase drug safety assessment requires in-depth hazard identification and integrated experimental approaches to address target and lead compound risks to support target assessment, candidate prioritization, candidate selection, and derisking of safety flags from in vitro, animal, and clinical testing. Consequently, the application of innovative models and techniques that allow the identification of early hazards, prioritize chemical series, and steer chemical design and safety assessment should ideally be integrated into the early phases of the discovery process. Similarly, mechanistic insight into animal and clinical drug toxicities can be critical in developing informed human risk assessment. In this session, we will present case studies of innovative investigative discovery phase toxicology that have enabled mechanistic understanding and improved quantitative human risk assessment. Examples will include the use of recombinant proteins and antibodies to probe the effects of small molecule candidate drugs on in vivo safety biomarkers, use of 3D microphysiological models of human and animal organs, transcriptomics, drug metabolism, and modeling and simulation techniques to quantify translational risk assessment to humans.

Introduction. Clay Scott, AstraZeneca, Waltham, MA.


Reduced Kupffer Cell Clearance Is Causing Elevation of Serum Toxicity Biomarkers in Rat and Monkey in Absence of Organ Injury. Francois Pognan, Novartis, Basel, Switzerland.

Use of Early Phenotypic In Vivo Markers to Assess Human Relevance of an Unusual Rodent Non-Genotoxic Carcinogen In Vitro. Adrian Roth, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Characterization and Mechanistic Investigation of Hemolytic Anemia in Rats Induced by an Early Small Molecule Oncology Candidate. Howard Mellor, Vertex Pharmaceuticals, Oxford, United Kingdom.


Panel Discussion/Q&A.
Data for Chemical Evaluations: Secret or Otherwise

Monday, March 11, 12:10 PM to 1:30 PM

Chairperson(s): Jane Vergnes, Bergeson & Campbell, PC, Washington, DC; and Lynn Bergeson, Bergeson & Campbell, PC, Washington, DC.

Primary Endorser: Ethical, Legal, Forensics, and Societal Issues Specialty Section

In April 2018, US EPA requested comment on its proposed Strengthening Transparency in Regulatory Science Rule (Strengthening Transparency Rule). The proposal goes to the heart of information used for significant regulations: specifically, “the dose response data and models that underlie what we are calling ‘pivotal regulatory science.’ ‘Pivotal regulatory science’ is the studies, models, and analyses that drive the magnitude of the benefit-cost calculation, the level of a standard, or point-of-departure from which a reference value is calculated.” US EPA intends the rule to provide this transparency “in a manner consistent with statutory requirements for protection of privacy and confidentiality of research participants, protection of proprietary data and confidential business information, and other compelling interests.” US EPA “will use peer-reviewed information, standardized test methods, consistent data evaluation procedures, and good laboratory practices to ensure transparent, understandable, and reproducible scientific assessments.” Many have expressed support for the Strengthening Transparency Rule, stating that the requirement for transparency is long overdue. Others have expressed concern, including concerns about a potential for US EPA to handpick certain “public” studies and to discount other valid studies only because the submitters did not divulge all of the confidential data. Similarly, concerns have been expressed regarding the inability to protect important confidential information such as patient identity. The proposed rule is controversial and will be the subject of debate (which is likely to be ongoing in March 2019) and significant comment. What this raises is a fear that addressing some concerns about how air regulations are justified might have unintended consequences in other US EPA media programs. US EPA review of epidemiology data underlying its conclusions may be subject to more stringent requirements than it previously was. This session will consider legal, scientific, ethical, and policy issues pertinent to the proposal and consider broader issues pertinent to the use of data for chemical evaluations. Similarly, the proposed rule is expected to significantly impact rulemakings under the Toxic Substances Control Act (TSCA), the Clean Air Act (CAA), and the Safe Drinking Water Act (SDWA), each of which requires US EPA to rely on the best available science. Data that are protected by medical privacy restrictions, and on which US EPA has historically relied in many rulemaking contexts, could be disallowed under a broad reading of the proposal. Several nongovernmental organizations have already expressed concern over this interpretation and believe that US EPA could be acting in an arbitrary and capricious manner if it relied on some confidential data for Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) purposes while disallowing medical data for CAA purposes. These, and many other issues, are expected to be raised during the comment period.

Introduction. Jane Vergnes, Bergeson & Campbell, PC, Washington, DC.

Regulatory Background. Lynn Bergeson, Bergeson & Campbell, PC, Washington, DC.

Public Policy/Public Health/Quality of Regulatory Science Perspective. Lynn Goldman, George Washington University, Washington, DC.


What If the Strengthening Transparency Rule Were Adopted for All Decision-Making? Jonathan Samet, Colorado School of Public Health, Aurora, CO.

Panel Discussion/Q&A.
Electronic Waste: An Evolving Global Health Concern and Risk Assessment Challenge

Monday, March 11, 12:10 PM to 1:30 PM

Chairperson(s): Babasaheb (Bob) Sonawane, TRACS, LLC, North Potomac, MD; and Michelle Heacock, NIEHS, Research Triangle Park, NC.

Primary Endorser: Mixtures Specialty Section

Other Endorser(s): Metals Specialty Section; Risk Assessment Specialty Section

As the demand for electronics increases, the amount of electronic waste (e-waste) steadily accumulates at a rapid pace. An estimated 65 million tons of e-waste were created globally in 2017, with further increases projected in the years ahead. E-waste is composed of an alarming combination of several hazardous substances. A systematic review looking at health outcomes related to e-waste exposure showed that increases in spontaneous abortions, stillbirths, and premature births, and reduced birth weights and birth lengths, are associated with exposure to e-waste. Direct and indirect exposures are a threat to human health and vulnerable groups such as fetuses, children, pregnant women, the disabled, and workers in the informal sector. Because of this threat, they need specific protection. The majority of e-waste recycling is conducted in low-to-middle-income countries informally, by workers using primitive techniques such as burning, with little or no safeguards in place for human and environmental health. This session will provide an overview of the e-waste problem and present research findings from studies conducted in India and Vietnam. The session will end with a presentation that will discuss the multi-factorial problem of e-waste due to limited studies and the multiple routes of exposure to multiple classes of hazardous substances in the context of vulnerable populations. These presentations will inform a panel that will discuss risk assessment challenges (exposures to a mixture of chemicals from multiple sources) and provide a forum to discuss strategies to reduce exposures to e-waste.

Introduction. Babasaheb (Bob) Sonawane, TRACS, LLC, North Potomac, MD.

E-waste: Challenges and Opportunities toward Reducing Exposures. Brittany Trottier, NIEHS, Research Triangle Park, NC.

Crude Electronic Waste Recycling by the Informal Sector Is a Potential Source for a Cocktail of Toxicants in Indian Cities: Atmospheric Transport Models and Health Risk Assessment. Paromita Chakraborty, SRM Institute of Science and Technology, Kattankulathur, India.

Biomonitoring of Female Vietnamese Electronic Waste Recyclers for Selected Metals and Organics. Linda Birnbaum, NIEHS/NTP, Research Triangle Park, NC.

Toxicity of Metal and Metallic Compounds and E-waste Chemical Mixtures. Bruce Fowler, Emory University School of Public Health, Atlanta, GA.

Panel Session. Babasaheb (Bob) Sonawane, TRACS, LLC, North Potomac, MD.
Federal Efforts in Rapidly Assessing Hazard and Risk to Emerging Threats and Emergency Response

Monday, March 11, 12:10 PM to 1:30 PM

Chairperson(s): Michael DeVito, NIEHS/NTP, Research Triangle Park, NC; and Reeder Sams, US EPA, Research Triangle Park, NC.

Primary Endorser: National Capital Area Regional Chapter

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section

Under the authorization of a variety of federal statutes, several federal agencies are involved in protecting public health from emerging environmental threats and in emergency response. These federal agencies have developed programs that can provide regulators with a rapid assessment of the potential hazard and risk associated with exposures in times of emergency response. These approaches combine rapid literature assessments, computational toxicology, and in vitro toxicology. These same approaches are also being applied to evaluate emerging issues related to chemical exposures. This session will highlight these efforts at the US Department of Defense, the Agency for Toxic Substances and Disease Registry, the US EPA, and the NIEHS National Toxicology Program.


Screening for Potential Health Risks in Impacted Communities at the Agency for Toxic Substances and Disease Registry. William Cibulas, CDC/ATSDR, Atlanta, GA.


The National Toxicology Program’s Rapid Evaluation and Assessment of Chemical Toxicity (REACT) Program. Michael DeVito, NIEHS/NTP, Research Triangle Park, NC.

SOT invites its sister societies from around the world to participate in the Global Gallery of Toxicology.
Immune-Epithelial Cell Crosstalk in Lung Toxicology and Disease

Monday, March 11, 1:45 PM to 4:30 PM

**Chairperson(s):** Alessandro Venosa, University of Pennsylvania, Philadelphia, PA; and Andrew Gow, Rutgers, The State University of New Jersey, Piscataway, NJ.

**Primary Endorser: Immunotoxicology Specialty Section**

**Other Endorser(s):** Inhalation and Respiratory Specialty Section

Understanding the mechanisms involved in mediating the pollutant-based deficits in pulmonary health remains an area of continued interest within SOT and in the field of public health. The lung represents a unique toxicological target due to its continuous exposure to the gaseous components of the environment and its function as a major first pass organ. The environment of the lung surface is a unique system consisting of both barrier and immunological defenses. A key aspect of the system is the interaction between resident cells of the lung (both parenchymal epithelial cells and resident immune subsets) and recruited inflammatory cells. It is the goal of this session to address the molecular mechanisms involved in the resident/recruited response to toxicants. Therefore, the session will highlight current developments in the fields of lung biology, immunotoxicology, and pharmacology. The pulmonary response to toxicant exposure consists of a number of complex processes, including direct cellular injury, inflammation, and resolution. Much of this response is regulated by the resident cells of the lung surface, including both type I and type II epithelial cells and the alveolar macrophages. Proper recruitment and activation of circulating inflammatory cells is essential to mount the appropriate inflammatory and resolution responses. Therefore, epithelial-immune crosstalk is critical in the regulation of the pulmonary response to toxicants. To this end, high-throughput phenotyping of resident and infiltrating cells has highlighted novel pathways involved in cell-cell communication during progression and resolution of lung injury. These data, paired with characterization of temporal and spatial responses of immune cells, are pivotal to understand the mechanisms of chemical/environmental aggression. Although often neglected in several immunology studies, it is clear that lung epithelial cells intimately interact with resident immune subsets to activate (and dampen, when necessary) the appropriate inflammatory response following a diverse range of deleterious cues, including chemical/environmental (bleomycin, ozone, diesel particles), viral (influenza), and genetic (surfactant protein dysfunction). It is the goal of the session to inform the Society about the different cellular systems that exist within the lung and how signaling between these systems is critical in determining the consequences of toxicant exposure. In this session we will (1) highlight the role of epithelial type II cell stress in the initiation and modulation of pulmonary inflammation via intimate crosstalk with resident and peripheral inflammatory subsets; (2) examine the underappreciated role of the type I epithelial cell in controlling inflammation via extracellular vesicles in response to sterile stimuli (oxidative stress, cigarette smoke and acid aspiration) and infections (LPS/Gram negative bacteria); (3) link chromatin remodeling to specific responses to air pollutants (ozone) associated with exacerbation of inflammatory conditions; (4) evaluate the role age, sex, history of prior exposure, and antioxidant status play in lung epithelial cell response to nanoparticles, ozone, naphthalene, and particulate matter; and (5) characterize the mechanisms and effects of toxicant (ozone) exposure on production of specialized proresolving lipid mediators by resident and recruited monocyte/macrophage subsets. By describing these different aspects of cellular crosstalk, these presentations will offer a more insightful understanding of the lung dynamics following toxic exposure. In addition to discussing the most recent progress made in this area of research, speakers will address existing hurdles in our understanding of the lung-immune cell axis in experimental model and clinical therapy development.

**Introduction.** Andrew Gow, Rutgers, The State University of New Jersey, Piscataway, NJ.

**Alveolar Type II Cells Initiate and Modulate Inflammation in Lung Surfactant.** Alessandro Venosa, University of Pennsylvania, Philadelphia, PA.

**Extracellular Vesicle: An Emerging Mediator of Intracellular Crosstalk in Lung Inflammation and Injury.** Jin Yang, Boston University School of Medicine, Boston, MA.

**To Each Their Own: Molecular Mechanisms of Inter-Individual Variability in the Effects of Inhaled Toxicant Exposures.** Shaun D. McCullough, US EPA, Chapel Hill, NC.

(continued on next page)
Patterns of Co-exposure and Its Implications for Understanding the Health Effects of Mixtures

Monday, March 11, 1:45 PM to 4:30 PM

Chairperson(s): Thomas Webster, Boston University School of Public Health, Boston, MA; and Rogelio Tornero-Velez, US EPA, Research Triangle Park, NC.

Primary Endorser: Mixtures Specialty Section
Other Endorser(s): Exposure Specialty Section

While current chemical testing tends to focus on individual chemicals, the exposures that people actually experience involve mixtures of chemicals. The number of mixtures that can be formed from the thousands of environmental chemicals is enormous, and testing all of them would not be realistic. In recent years, the ongoing revolution in exposure science and analytic chemistry (e.g., non-targeted analysis) is permitting better assessment of exposures to more and more chemicals at lower cost. It appears likely that we will be facing the biggest data challenge in exposure science in the not very distant future, and novel statistical methods are needed for analyzing these data. Collaboration between mixtures toxicologists and exposure scientists has great promise. Exposure science has a very important role to play by (1) determining the combinations of chemicals to which people are actually exposed, reducing the combinatoric problem facing toxicologists; (2) identifying highly correlated exposures that might be better studied using whole mixtures methods than component-based methods; and (3) providing information needed by epidemiologists studying exposure to mixtures. A critical problem is understanding the patterns of exposure; for example, which exposures tend to occur together and how does this tendency depend on demographics and other factors? This session will bring together exposure scientists and mixtures toxicologists to examine methods for analyzing patterns of co-exposures; apply them to large datasets, such as National Health and Nutrition Examination Survey (NHANES) biomonitoring data and personal care product purchasing database; and discuss their implications for research on the health effects of exposure to mixtures in toxicology and epidemiology.

Hierarchical Structure of Patterns of Correlations between Biomarkers of Exposure and Their Implications for Studying the Health Effects of Mixtures. Thomas Webster, Boston University School of Public Health, Boston, MA.


Understanding and Predicting Patterns of Co-exposure. Rosemary Zaleski, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ.

Using Pregnancy Cohort Data to Identify Human-Relevant Mixtures for Experimental Evaluation in a Whole Mixture Risk Assessment Strategy. Chris Gennings, Icahn School of Medicine at Mount Sinai, New York, NY.

An Evaluation of HTS and Mixtures: From Component-Based to Whole Mixtures Studies. Michael DeVito, NIEHS/NTP, Research Triangle Park, NC.
Scaling Barriers: Cellular Dynamics and Models of Blood-Brain Barrier Developmental Toxicity

Monday, March 11, 1:45 PM to 4:30 PM


Primary Endorser: Reproductive and Developmental Toxicology Specialty Section

Other Endorser(s): Neurotoxicology Specialty Section; Scientific Liaison Coalition

This session will focus on a critical vascular interface, the blood-brain barrier (BBB), with regard to embryology and toxicology. The BBB is a core of the neurovascular unit (NVU) comprising microvascular endothelial cells, pericytes, astrocytes, microglia, and neurons. These cell types function in various capacities throughout development to regulate the distribution of substances from the circulatory system to the developing brain (i.e., toxicokinetics). Although historically described as “leaky,” the leading perspective in the field has recently shifted toward an understanding that the BBB is functional soon after it forms. BBB research tends to focus on toxicokinetics, but less is known about the toxicodynamic impact that drugs and chemicals may have on the developing BBB. Moreover, it is unclear whether such impacts would lead to developmental neurotoxicity (DNT). Evidence from mouse models and human genetics suggests that altered BBB development and function have a role in the etiology of neurobehavioral disorders such as autism spectrum disorder, supporting the hypothesis that chemical disruption of the developing BBB may also lead to DNT. While current models representing the state-of-the-science in this field have not demonstrated a direct link between BBB perturbation by chemical exposures and subsequent DNT, this hypothesis remains to be adequately tested. Alternative models may provide tools toward understanding this “black box” in BBB toxicology. This session will address the integrative biology and systems toxicology underlying BBB toxicodynamics and highlight the cutting-edge \textit{in vivo}, \textit{in vitro}, and \textit{in silico} models currently utilized for early life-stage considerations. The presenter lineup will begin with an overview that frames the importance, yet paucity, of developmental BBB research, followed by talks progressing from \textit{in vivo} to \textit{in vitro} and \textit{in silico} BBB models. The first Co-Chair will provide an introduction to the session theme by describing key cell types and timing of embryonic BBB development across species. This introduction will also briefly cover other areas of the brain (e.g., circumventricular organs) and their barriers; provide an overview of the state of the art in BBB models that will be described in more detail by the session presenters; and briefly survey traditional, toxicokinetic models and BBB transporters. The first presentation will introduce the cortical BBB and describe a mammalian \textit{in vivo} model used to investigate the role of microglia in establishing BBB integrity during embryonic development. The next presenter will discuss an embryonic, transgenic zebrafish model being used to investigate the role of pericytes in mediating developmental BBB toxicity. The next presenter will introduce a 3D \textit{in vitro} model designed to test BBB permeability to therapeutic antibodies. The final presentation will discuss novel multiscale \textit{in silico} models for unraveling complex cellular dynamics of BBB development in a computational neurovascular unit (cNVU) system, whereby toxicity pathways interact with fundamental morphoregulatory signaling (e.g., Wnt, Shh, Delta/Notch) during windows of vulnerability to developmental neurotoxicants. To wrap up the session, the second Co-Chair will emphasize the importance of establishing alternative BBB models that reduce animal testing, in addition to providing translational context for developmental BBB research by discussing the importance of these studies in relation to children’s environmental health protection.

\textbf{Introduction.} Katerine Saili, US EPA/NCCT, Research Triangle Park, NC.

\textbf{Applying a Mouse Model of Embryonic Macrophage Depletion to Elucidate the Role of Microglia in Blood-Brain Barrier Development.} Florent Ginhoux, Singapore Immunology Network (SIgN), Singapore, Singapore.

\textbf{Environmental Contaminant Exposure Reduces Pericyte Coverage of the Developing Cerebral Vasculature.} Jessica Plavicki, Brown University, Providence, RI.


\textbf{Microglia Are Required for Anastomosis in a Computational Neurovascular Unit (cNVU).} Todd Zurlinden, US EPA/NCCT, Research Triangle Park, NC.

Strategic Development of Read-Across within the EU-ToxRisk Project and Beyond

Monday, March 11, 1:45 PM to 4:30 PM

Chairperson(s): Marcel Leist, University of Konstanz, Konstanz, Germany; and Russell Thomas, US EPA/ORD, Research Triangle Park, NC.

Primary Endorser: In Vitro and Alternative Methods Specialty Section

Other Endorser(s): Computational Toxicology Specialty Section; Regulatory and Safety Evaluation Specialty Section

EU-ToxRisk is an integrated European “flagship” program driving mechanism-based toxicity testing and risk assessment for the 21st century. To support the paradigm shift in human risk assessment away from the traditional in vivo animal studies and toward new approach methodologies (NAMs), EU-ToxRisk, with its almost 40 partners and $40 million funding, focuses on two areas: repeat-dose systemic toxicity, using the lung, kidney, liver, and nervous system as examples of potential target organs; and developmental and reproductive toxicity. NAMs include different approaches such as in vitro, ex vivo, or ‘omics technologies and in silico and toxicokinetic modeling. The integration of NAM data into a risk assessment strategy is challenging, in particular for complex endpoints, such as repeat-dose or reproductive toxicity. This session, we will provide a view across the Atlantic; we will provide an in-depth overview and then demonstrate opportunities of the use of read-across, starting with an EU regulatory perspective and then broadening the scope to the most up-to-date developments from the EU-ToxRisk program. A focus is set on read-across case studies, by which the use of NAMs and mechanistic data is demonstrated. While the majority of techniques used within EU-ToxRisk is already well established, the project also invested into the development of new in silico prediction models. In addition, the session will address automated read-across (RASAR: read-across-based structure activity relationships) and Good Read-Across Practices. Session organizers believe that the learnings from the reported proof of concept read-across approaches will help to develop new mechanism-based chemical safety testing strategies. An early discussion on the limitations and advances of such approaches with the scientific community is needed to substantiate and support a paradigm shift in regulatory risk assessment practice.

Introduction. Marcel Leist, University of Konstanz, Konstanz, Germany.

Status of the EU-ToxRisk Project. Bob van de Water, Leiden University, Leiden, Netherlands.

Integration of NAMs in Risk Assessment: The Read-Across Approach of the EU-ToxRisk Project. Sylvia Escher, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany.

International Acceptance of Read-Across Based on NAMs. Henricke Kamp, BASF SE, Ludwigshafen, Germany.

Automated Read-Across and Good Practices. Thomas Hartung, Johns Hopkins University Center for Alternatives to Animal Testing (CAAT), Baltimore, MD.

A View across the Atlantic: Synopsis and Opportunities. Suzanne Fitzpatrick, US FDA, College Park, MD.

Panel Discussion/Q&A.
The two-year rodent cancer bioassay has been the standard regulatory requirement to predict carcinogenicity following human exposure to chemicals, including industrial chemicals and agrochemicals, food additives, pharmaceuticals, and environmental pollutants. Decades of experience conducting the bioassay and a better understanding of biology and cancer pathogenesis have led to questions about the scientific limitations and usefulness of the bioassay, especially in light of the resources, time, and animal use associated with the test. Moreover, further questions on the relevance of these data to assess human health risk arise due to the use of very high dose levels in these studies, which are several orders of magnitude higher than real-world human exposures. To address concerns over the human relevance of the assay, a shift in thought process has paved a path to many cross-sector efforts to rethink carcinogenicity assessment. The first presentation will provide a historical perspective on development and adoption of the rodent cancer bioassay and more recent efforts to modernize testing in this area. The second presentation will focus on alternative testing methods to carcinogenicity assessment to improve the efficiency of chemical risk assessment and produce data that are more relevant to protecting human health. The third presenter will share a global perspective on efforts to develop integrated approaches to testing and assessment and adverse outcome pathways to better understand the mechanisms that lead to carcinogenicity in humans and that can be used to design alternatives to the currently used bioassay. The fourth presentation will describe a decision tree and criteria developed within the agrochemical sector and share the results of how they have been used to retrospectively analyze the need for the cancer bioassay in regulatory decision-making. The final presentation will share the US EPA Office of Pesticide Programs’ perspective on alternative methods of testing, including a weight of evidence approach incorporating all the relevant data available including exposure, and will share their vision going forward on waiver criteria for rodent cancer bioassays. Overall, the session will include presentations from scientists across different sectors and enable a panel discussion between the speakers and audience on the value of the cancer bioassay, which has been used as the gold standard for decades by global regulatory bodies despite being resource, time, and animal intensive. Finally, the session will discuss alternative approaches that could be used to assess carcinogenicity, identifying remaining gaps and shedding light on ongoing global efforts on this subject.

Introduction. Sabitha Papineni, Corteva Agriscience, Indianapolis, IN.

History of the Rodent Cancer Bioassay in Chemical Risk Assessments and What Did We Learn? A. Wallace Hayes, University of South Florida, Tampa, FL, and Michigan State University, East Lansing, MI.

Alternative Testing Paradigms to Assess Chemical and Pharmaceutical Carcinogenicity. Charles Wood, Boehringer Ingelheim Pharmaceuticals, Inc., Durham, NC.

Moving Forward in Carcinogenicity Assessment: An International Perspective. Raffaella Corvi, EURL ECVAM, Ispra, Italy.

A Weight of Evidence Approach to Assess Carcinogenicity Potential and Retrospective Analysis of Agrochemicals. Sabitha Papineni, Corteva Agriscience, Indianapolis, IN.

Commitment at the US EPA/OPP to Reduce and Replace Animal Use: Looking at Carcinogenicity and Beyond. Gregory Akerman, US EPA, Washington, DC.

Panel Discussion/Q&A.
A Tale of an In Vitro Method: From Inception to International and Regulatory Acceptance

Monday, March 11, 1:45 PM to 4:30 PM

Chairperson(s): Audrey Turley, Nelson Laboratories LLC, Salt Lake City, UT; and Kelly Coleman, Medtronic plc, Minneapolis, MN.

Primary Endorser: Medical Device and Combination Product Specialty Section

Other Endorser(s): In Vitro and Alternative Methods Specialty Section

In vitro alternative test methods sound promising but can often be difficult to implement on a global scale in a way that will be truly impactful. This is a tale of success for one such method. Medical devices are evaluated for biological safety in accordance with the ISO 10993 biocompatibility standards. Every medical device, irrespective of its nature or body contact, must be assessed for its potential to cause cytotoxicity, irritation, and sensitization. Historically, cytotoxicity was the only approved in vitro method. However, over the past decade an in vitro irritation method using reconstructed human epidermis (RhE) was validated for pure chemicals as described in OECD 439. It seemed logical that this method, with a few adjustments, could also be used to assess medical device extracts. Introducing this test as the preferred method to address the irritation potential of medical devices will greatly reduce the number of animals used for the biological safety assessment of medical devices and combination products prior to market release. This session will present the monumental collaboration that took place to bring the in vitro irritation method for medical devices to the industry, including manufacturing an extractable positive control, designing and performing an international interlaboratory round-robin study, and presenting of tools to fast-track the method into regulatory acceptance.

Introduction to Session. Audrey Turley, Nelson Laboratories LLC, Salt Lake City, UT.

Introduction to Presenters. Kelly Coleman, Medtronic plc, Minneapolis, MN.

Time for a Change: The ISO 10993 Standards and Irritation Testing of Medical Devices. Kelly Coleman, Medtronic plc, Minneapolis, MN.

Modification and Use of Reconstructed Human Epidermis (RhE) Models. Audrey Turley, Nelson Laboratories LLC, Salt Lake City, UT.

Creating Irritant-Infused Polymers for Extraction and Irritation Analysis. Beau Rollins, ConvaTec, Greensboro, NC.

The Application of Reconstructed Human Epidermis (RhE) Models as In Vitro Skin Irritation Tests for Detection of Irritant Activity in Medical Device Extracts. Wim De Jong, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands.

Applying Systems Biology Approaches to Understand the Joint Action of Chemical and Nonchemical Stressors

Monday, March 11, 1:45 PM to 4:30 PM

Chairperson(s): Cynthia Rider, NIEHS/NTP, Research Triangle Park, NC; and Julia Rager, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Primary Endorser: Mixtures Specialty Section

Other Endorser(s): Molecular and Systems Biology Specialty Section; Women in Toxicology Special Interest Group

Toxicology has evolved from a strictly observational science to a more predictive one that relies on knowledge of stressors (chemical or nonchemical) and the biological systems with which those stressors interact to identify health hazards. Furthermore, the introduction of the exposome concept brought into sharp focus the fact that humans are routinely exposed to a great number of chemical and nonchemical stressors over the course of a lifetime. Chemical stressors can arise from everyday use of personal care products and consumer products, occupational exposures, and exposure to pollutants through contaminated air, water, and/or food. Nonchemical stressors include physical stressors (e.g., heat and cold, radiofrequency radiation, biological agents such as allergens and viruses), and psychosocial stressors (e.g., noise, exposure to violence), which involve both exposure and perception. The traditional reductionist view reflected in toxicology by the study of one chemical at a time falls short of the promise of high-throughput technologies, a focus on biological pathway disruption, and acknowledgement that real-world exposures are complex. In response to the evolution of our thinking in toxicology and exposure science, a rational approach to address the challenges of mixtures has emerged. This conceptual framework incorporates systems biology and mixtures toxicology. Mixtures toxicology refers here to predictive models of how stressors can act when they are present concurrently, exemplified by concepts of dose addition and response addition. The starting place of this conceptual framework is the disease or endpoint of interest. Next, the adverse outcome pathways that converge at that disease are described as a network of intersecting pathways that lead from multiple molecular initiating events or key events to a single apical target. Chemicals or nonchemical stressors that are known to disrupt those pathways are identified. Finally, we can develop and test hypotheses of how those stressors might contribute to development of the disease or adverse outcome of interest. Recently, several independent groups have developed projects or case studies to work through this conceptual framework. Examples of endpoints include disruption of male reproductive tract development, atherosclerosis, steatosis, and cancer. Although these efforts are in various stages of development, a detailed review of the available programs will provide opportunities to identify challenges and knowledge gaps, share information, and foster collaboration and cooperation to move the field forward. Case studies, such as the ones presented here, will inform cumulative risk assessment by providing a path forward for determining which stressors to include and how we might move away from a chemical-centric perspective to one focused on the diseases that are of greatest concern to public health.

Understanding Biological Pathways across Toxicological Tools. Julia Rager, University of North Carolina at Chapel Hill, Chapel Hill, NC.


A Model Disease to Determine the Interaction of Chemical and Nonchemical Stressors. Danielle Carlin, NIEHS, Research Triangle Park, NC.

The EuroMix Project on Mixtures That Target Steatosis. Alfonso Lampen, BfR, Berlin, Germany.

Converging on Cancer with Systems Toxicology. Cynthia Rider, NIEHS/NTP, Research Triangle Park, NC.

Panel Discussion/Q&A.
Active renal secretion in the proximal tubules is a major drug elimination route, making the kidney susceptible to drug-induced injury. High blood flow to the kidneys significantly contributes to exposure to potential nephrotoxins that enter the cells mostly basolaterally via organic anion and organic cation transporters or apically via reabsorption processes. Many drugs associated with proximal tubule damage are polar, such as acyclovir (cLogP -2.2) and cidofovir (cLogP -2.0), exhibiting poor passive permeability, and hence require active transporters or receptors. To investigate the nephrotoxic potential of lead compounds, in vitro systems should emulate the renal physiologic environment, including functional transport machinery. Cell lines or primary cells traditionally used in 2D kidney toxicity screening lack the appropriate transporter expression, in vivo structure, and function and are unable to predict preclinical/clinical kidney toxicity. Recent biotechnological developments provide more sophisticated and promising models, including 3D culture platforms and reprogrammed proximal tubule cells, which could be utilized to create a more physiologically relevant platform with the potential to improve the prediction value for proximal tubule toxicity screening. The session will provide a general overview of these state-of-the-art biotechnological advances to facilitate the discussion about the path forward for in vitro kidney toxicity screening with high reliability and mechanistic insight.

**Introduction.** Shuyan Lu, Pfizer Inc., San Diego, CA.

**Early Screening for Nephrotoxicity Employing Transporter Overexpression Cell Lines.** Shuyan Lu, Pfizer, Inc., San Diego, CA.

**Directly Reprogrammed Induced Renal Tubular Cells (iREC) for Renal Toxicity Testing.** Soeren Lienkamp, University Medical Center Freiburg, Freiburg, Germany.

**Challenge Accepted: Update on NC3R NephroTube Challenge.** Martijn Wilmer, Radboudumc, Nijmegen, Netherlands.

**Microphysiological Model of Human Kidney Proximal Tubule for Toxicity Screening.** Edward Kelly, University of Washington, Seattle, WA.

**3D Vascularized Kidney-on-Chip Models for In Vitro Drug Toxicity Studies.** Jennifer Lewis, Harvard University, Cambridge, MA.

**Panel Discussion/Q&A.**
Models and Strategies for Building Diversity and Inclusion in Toxicology

Monday, March 11, 4:30 PM to 5:50 PM

Chairperson(s): Christine Perdan Curran, Northern Kentucky University, Highland Heights, KY; and José Manautou, University of Connecticut School of Pharmacy, Storrs, CT.

Primary Endorser: Education Committee

Other Endorser(s): Committee on Diversity Initiatives; Hispanic Organization of Toxicologists Special Interest Group

Diversity and inclusion in science are more than a strategic goal for universities, government labs, and industry. Recent findings demonstrate that diverse scientific teams produce more innovative science and more highly cited publications. However, many institutions struggle with implementing effective programs to increase representation by women, underrepresented minorities, and those from countries with fewer educational and scientific resources. This session will bring together leading experts from the Society of Toxicology, the National Institutes of Health, and the University of Maryland, Baltimore County’s Meyerhoff Scholars Program to share successful models and strategies for recruitment and retention of STEM trainees and career development toward independent research careers. The topics to be discussed include (1) an overview of the SOT Undergraduate Diversity Program’s 30 years of experience in recruiting new toxicology trainees and the Committee on Diversity Initiatives’ efforts to expand global opportunities in toxicology training, (2) the NIH perspective on supporting career success in biomedical research where the number of underrepresented minority trainees is increasing while success at the early career stage is lagging, (3) the successful implementation of the Meyerhoff Scholars Program, which encourages positive peer pressure among highly capable underrepresented minorities and structured mentoring toward advanced degrees in STEM fields, and (4) guidance on successfully navigating a career transition from academy to industry. The session will conclude with questions from the audience and a general discussion of inclusion and diversity in toxicology training and mentoring.

SOT’s Diverse Efforts to Promote Diversity and Inclusion in Toxicology Education and Training. José Manautou, University of Connecticut School of Pharmacy, Storrs, CT.

NIH’s Scientific Approach to Achieving Inclusive Excellence. Hannah Valantine, NIH Scientific Workforce Diversity Office, Bethesda, MD.

The Meyerhoff Scholars Program: Successful Approaches for Promoting Inclusive Excellence in STEM. Michael Summers, University of Maryland, Baltimore County, Baltimore, MD.

Reach Back as You Climb: A Personal Journey from Academia to a Career in Drug Development. Elise Lewis, Charles River Laboratories, Horsham, PA.
“Not Your Father’s ED”: Expanding the Definition and Understanding of Endothelial Dysfunction (ED) Due to Inhaled Toxicants

Tuesday, March 12, 8:00 AM to 10:45 AM

Chairperson(s): Daniel Conklin, University of Louisville, Louisville, KY; and Matthew Campen, University of New Mexico, Albuquerque, NM.

Primary Endorser: Cardiovascular Toxicology Specialty Section

Other Endorser(s): Inhalation and Respiratory Specialty Section; Stem Cells Specialty Section

Endothelial Dysfunction (ED) has referred traditionally to any decrement in endothelium-dependent vascular function. This typically involves nitric oxide (NO) production/signaling, as NO is one of the most ubiquitous messengers. This selective definition remains important today, as loss of NO production/bioavailability can contribute to any number of pathological sequelae, including hypertension, erectile dysfunction, and thrombogenesis/stroke. Our understanding of endothelium biology and ED now incorporates other dysfunctional changes, including angiogenesis, vascular permeability, release of matrix metalloproteinases (MMPs), expression of adhesion proteins, and loss of endothelial repair, to name a few, into an ever more inclusive definition of ED. New technologies and tools applied in the assessment of said functions have spurred innovative measures of myriad ED-related outcomes and a better appreciation of the functional capacity of endothelium. The session will span a continuum of complementary methodological approaches, from flow-mediated dilation in humans to angiogenesis assays in vitro and in vivo. As an overall theme for exploring emergent measures of ED, the symposium will focus on ED induced by inhaled toxins, which provides a real-world, contemporary problem and an unresolved mystery by which inhaled air toxics (air pollution, nanoparticles, e-cigarette aerosols) exert extrapulmonary influence over the systemic endothelium.

Introduction. Christopher Wingard, Bellarmine University, Louisville, KY.

Diverse Methodological Approaches to Investigate the Endothelial Impacts of Toxicants and Systemic Inflammation. Matthew Campen, University of New Mexico, Albuquerque, NM.

Flavoring Additives in Tobacco Products Induce Endothelial Cell Dysfunction. Jessica Fetterman, Boston University, Boston, MA.

Air Pollution and Endothelial Progenitor Cells (EPCs): Measuring Loss of Endothelium Repair Function. Daniel Conklin, University of Louisville, Louisville, KY.

Endothelial Heterogeneity: Diverse Anatomic and Physiologic Determinants of Toxicological Assessments after Inhalation Exposures. Timothy Nurkiewicz, West Virginia University, Morgantown, WV.

Moderated Panel Discussion. Christopher Wingard, Bellarmine University, Louisville, KY.
Stem Cells and Metals Toxicity: From Tissue Regeneration and Repair to Carcinogenesis

Tuesday, March 12, 8:00 AM to 10:45 AM

Chairperson(s): Erik Tokar, NIEHS/NTP, Research Triangle Park, NC; and Aaron Barchowsky, University of Pittsburgh, Pittsburgh, PA.

Primary Endorser: Stem Cells Specialty Section

Other Endorser(s): Mechanisms Specialty Section; Metals Specialty Section

Humans are exposed to metals on a daily occurrence. These exposures can occur during all stages of life, and could result in toxic effects in all organ systems, leading to aberrations in development and other biological processes. Stem cells (SCs) are highly specialized cells that are found in nearly all tissues and organs. Alterations in normal SC functions can adversely affect development and health, and can play key roles in disease etiology. The objective of this session is to highlight the various ways that metals can target and alter SCs during biological processes such as differentiation, tissue repair and regeneration, and carcinogenesis. The first presentation will focus on how chronic arsenic exposure alters muscle SC function to diminished regeneration, and how the effects of this metalloid on the microenvironment appear to play a key role in these alterations. The second presentation will discuss the effects of early-life methyl mercury exposure on muscle development and resultant motor function deficits, including the key roles of several candidate genes that act at the level of muscle SCs and/or regulate myocyte differentiation, mitochondrial biogenesis, and mtDNA transcription. The third talk will describe how subchronic manganese exposure affects adult neurogenesis by reducing the number of neural SCs in the hippocampal dentate gyrus and inhibiting the differentiation of neural stem/progenitor cells to mature neurons. The implications of these effects in Parkinson’s disease will be presented. The fourth presentation discusses how arsenic targets SCs and alters SC signaling pathways during carcinogenesis and the emerging evidence of how the metalloid can “recruit” SCs via altering exosome cargo and the tumor microenvironment. The final presentation focuses on how the stage of life during cadmium exposure can lead to differences in the number of breast SCs and their differentiation. Mechanisms underlying these differences and in breast cancer formation induced by this heavy metal will be presented. This session will be of interest to scientists involved in SCs, metals, development, or cancer research, and will be ideal for those who desire mechanistic understanding of the pathogenic and toxic effects of metals on SCs.

Introduction. Aaron Barchowsky, University of Pittsburgh, Pittsburgh, PA.

Arsenic-Induced Alterations in the Muscle Extracellular Matrix Drive Stem Cell Dysfunction and Impaired Regeneration. Fabrisia Ambrosio, University of Pittsburgh, Pittsburgh, PA.

Muscle Stem Cells and Myogenic Targets of Methylmercury Toxicity. Matthew Rand, University of Rochester School of Medicine and Dentistry, Rochester, NY.

Toxicity of Mn Exposure on Neural Progenitors and Adult Neurogenesis. Wei Zheng, Purdue University School of Health Sciences, West Lafayette, IN.

Stem Cells and the Microenvironment in Arsenic Toxicity and Carcinogenesis. Erik Tokar, NIEHS/NTP, Research Triangle Park, NC.

Systems Toxicology Approaches to the Science of Safety Evaluation  
Tuesday, March 12, 8:00 AM to 10:45 AM  
Chairperson(s): Myrtle Davis, Bristol-Myers Squibb, Princeton, NJ; and Cynthia Afshari, Amgen, Thousand Oaks, CA.  
Primary Endorser: Clinical and Translational Toxicology Specialty Section  
Other Endorser(s): Mechanisms Specialty Section; Regulatory and Safety Evaluation Specialty Section  

Systems toxicology is a transformational subdiscipline within toxicology that applies approaches from systems biology to toxicology-related questions. The session will bring together several advances within systems toxicology that are focused on diverse applications and opportunities in drug safety. Each presenter will share examples of successes and challenges they have experienced with applying ‘omic methods, definitive approaches (e.g., CRISPR, knockouts/ins), and network analysis to toxicology evaluations. The first talk will provide an overview of the challenges inherent in extrapolating safety signals across species to understand human risk. Immune responses provide a natural model to facilitate our understanding of complex and interactive events, and the second talk will address immunotoxicity in the context of systems approaches that can be applied to understanding the complexity of immune system interactions. The third presentation will focus on the promise and challenges of microphysiological platforms in systems toxicology. The final talk will provide mechanistic insights into species-specific metabolism, with emphasis on how systems approaches can facilitate the selection of biomarkers consistent with rat and human biology. Key insights about how computational models can serve as platforms for contextualizing experimental data and making functional predictions will be shared. The collective content of the session will highlight how we might use sophisticated, integrated systems and modeling to inform safety decisions in drug discovery.

The Immune System in the Context of Systems Toxicology. Wendy Freebern, Bristol-Myers Squibb, New Brunswick, NJ.
Application of a Microphysiology (MPS) Platform for Systems Toxicology. D. Lansing Taylor, University of Pittsburgh, Pittsburgh, PA.
Reconciling Rat and Human Liver Genome Scale Metabolic Networks. Jason Papin, University of Virginia, Charlottesville, VA.

Using Zebrafish as a Model to Understand and Ultimately Prevent Neurotoxicity  
Tuesday, March 12, 8:00 AM to 10:45 AM  
Chairperson(s): Jessica Plavicki, Brown University, Providence, RI; and Tamara Tal, US EPA/NHEERL, Durham, NC.  
Primary Endorser: Molecular and Systems Biology Specialty Section  
Other Endorser(s): Neurotoxicology Specialty Section; Reproductive and Developmental Toxicology Specialty Section  

Brain health is essential for human well-being across all life stages. Brain development and function are impacted by both genetic and environmental factors. Environmental factors, including exposure to environmental contaminants, are implicated in the etiology of a number of developmental, psychiatric, and neurodegenerative disorders. The zebrafish is a powerful model for assessing the impact of toxicants on brain development and function. Zebrafish embryos are externally fertilized, which enables direct exposure of the developing embryo, obviating the requirement for maternal exposures. In addition, developing embryos are transparent, which allows for in vivo imaging of the developing brain. Overall, development occurs rapidly, including formation of the nascent nervous system by three days of life. Furthermore, a suite of behavioral assays have been developed as functional readouts of toxicant effects on nervous system development and function, and these have been routinely adapted to medium-to-high-throughput screens for hazard identification and chemical prioritization. In this session, researchers will describe how they have leveraged the zebrafish model to investigate different mechanisms of action by which toxicant exposure alters brain development and function. The first presentation will reveal the essentiality of the aryl hydrocarbon receptor (AHR) in blood-brain barrier (BBB) formation and how AHR agonists perturb BBB development. The second talk will introduce the microbiota-gut-brain axis and how developmental exposure to exogenous estradiol compromises neurobehavioral development in a microbiota-dependent manner. The third talk will illuminate the role of GABAergic perturbations...
by environmental chemicals using a gene editing approach. The fourth presentation will show a mechanistic link between domoic acid exposure, myelination defects, and impaired startle response. The fifth talk will highlight new analytical chemistry approaches that can be used to elucidate mechanisms by which xenobiotics disrupt cholinergic, serotonergic, dopaminergic/adrenergic, histaminergic, and glutaminergic/GABAergic neurotransmitter systems. An excellent 2018 zebrafish session surveyed the multiple uses for larval and adult zebrafish including screening environmental chemicals for developmental toxicity, identifying epilepsy drugs, examining chemical uptake, and the assessing of the effects of early-life chemical exposures on adult behavior or transgenerational epigenetic changes. This 2019 session, however, will focus solely on the developing nervous system and all presentations will be mechanistically focused. Attendees will be exposed to the basic biology underlying unique neurodevelopmental systems like the blood-brain barrier, microbiota-gut-brain axis, GABAergic neuronal activity, and axonal myelination. In addition, perturbation of these systems by toxicant exposures will reveal linkages between these core neurodevelopmental processes and phenotypic outcomes like hyperactivity, seizures, abnormal startle responses, and blood-brain barrier maintenance and function.

Introduction. Tamara Tal, US EPA/NHEERL, Durham, NC.

Zebrafish as a Model for Studying Toxicant-Induced Neurovascular Malformations and Blood-Brain Barrier Dysfunction. Jessica Plavicki, Brown University, Providence, RI.

Estradiol Exposure Disrupts the Microbiota-Gut-Brain Axis during Zebrafish Development. Tara Catron, BASF Corporation, Research Triangle Park, NC.

Using Larval Zebrafish as a Model Organism to Study Chemical-Induced Seizures. Dennis Carty, University of California Davis, Davis, CA.

Early Developmental Exposure to Low Levels of Domoic Acid, a Harmful Algal Bloom Toxin, Disrupts Myelination, Leading to Behavioral Effects. Jennifer Panlilio, MIT/Woods Hole Oceanographic Institution (WHOI), Woods Hole, MA.


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Emergent Mechanisms of Cytochrome P450 Gene Regulation: Defining an Improved Roadmap toward 21st-Century Pharmacogenomics

Tuesday, March 12, 8:00 AM to 10:45 AM

Chairperson(s): Andrew Annalora, Oregon State University, Corvallis, OR; and Patrick Iversen, LS Pharma, LLC, Lebanon, OR.

Primary Endorser: Molecular and Systems Biology Specialty Section

Other Endorser(s): Mechanisms Specialty Section

To understand the interplay between nuclear receptor (NR) signaling and the expression of phase I, II, and III drug metabolizing systems, one must appreciate the role that endo-xenobiotic exposures play in organizing both gene expression and alternative gene splicing events. The human transcriptome is shaped by an array of different factors, including genetics, chemical exposures, diet, and metabolic diseases; this complex process is mediated primarily by differential recognition of gene promoters and canonical splice-sites by either the DNA Polymerase II transcriptional complex or the spliceosome; the structural organization of these multi-subunit, gene-processing complexes are subject to modulation by ligand-activated NR proteins that allow highly specific cellular responses to chemical or microbial invasion. Systems approaches are quickly expanding our ability to assess the impact of endo-xenobiotic exposures on gene expression and metabolism. The goal of the session is to integrate cutting-edge research focused on various systems approaches to toxicology that are providing novel insights into the global determinants of Cytochrome P450 (CYP) gene regulation as needed to synthesize a more coherent model of NR-mediated regulation of both transcription and gene splicing. The workshop will highlight research aimed at deconvoluting the overlapping contributions that endogenous substrate, xenobiotic, and microbiome-mediated metabolism play in crafting cellular responses to the environment, in pursuit of an improved pharmacogenomic framework for advancing both predictive toxicology and precision-based approaches to medicine. The presentations will also explore how alternative model systems, such as the organ-on-a-chip technology, are providing new opportunities to manipulate CYP gene expression and splicing in a highly personalized manner that promises to usher in a new era of safe and effective gene-directed therapeutics.

Introduction. Andrew Annalora, Oregon State University, Corvallis, OR.

Meta-Transcriptomics Analysis of Alternative Splicing in the Cytochrome P450 Superfamily: Decoding Novel Mechanisms of Gene Regulation and Function, Environmental Toxicity, and Disease. Andrew Annalora, Oregon State University, Corvallis, OR.

Gut Microbiome: A Novel Frontier for Xenobiotic Metabolism in the Host Liver. Julia Cui, University of Washington, Seattle, WA.

Intestinal Epithelial Cell Receptors as Modulators of Host-Microbiota Communication. Andrew Patterson, Pennsylvania State University, University Park, PA.


Developing the Human “Kidney-on-a-Chip”: An Enhanced Model System for Assessing Personalized Drug and Xenobiotic Toxicity. Edward Kelly, University of Washington, Seattle, WA.

Panel Discussion/Q&A.
Predicting Metabolic Clearance Rates for Drug Leads and Environmental Chemical Risk Assessment

Tuesday, March 12, 8:00 AM to 10:45 AM

Chairperson(s): Nisha Sipes, NIEHS/NTP, Research Triangle Park, NC; and Jon Arnot, ARC Arnot Research and Consulting Inc., Toronto, ON, Canada.

Primary Endorser: Biological Modeling Specialty Section

Other Endorser(s): Computational Toxicology Specialty Section; Risk Assessment Specialty Section

As the National Research Council (NRC) established in 1983, chemical risk assessment requires analysis of hazard, exposure, and the dose-response relationship, all three of which require toxicokinetic (TK) data that are often unavailable. To address this gap, in vitro high-throughput TK approaches have been developed to assess metabolic clearance rate, and fraction unbound, in plasma. However, while high(er) throughput, these in vitro approaches are still too slow to address all novel compounds and chemicals occurring in commerce and the environment. Several computational methods have been published for predicting plasma binding for pharmaceuticals and environmental spaces, but the prediction of metabolic rate has been more difficult. Libraries of TK data, largely obtained from in vitro assays, have been painstakingly obtained for many hundreds of chemicals. TK libraries are now being used as gold standards for developing methods to estimate TK for untested compounds. These methods draw inferences from chemical structure and physicochemical properties. If the uncertainty and domain of applicability can be characterized and quantified, then these methods would allow for a timely, risk-based prioritization strategy characterizing dose relationships between in vitro bioactivities and predicted human exposure.

Presenters will consider the state-of-the-science between traditional and higher-throughput methods, and the associations between them, such as extrapolation techniques, model confidence, acceptable uncertainty, and context applicability. Understanding the state-of-the-science in in silico toxicokinetics for government and industry applications will aid the inclusion of such techniques when limited data are available.


Quantitative Property-Property Relationship for Screening-Level Prediction of Intrinsic Metabolic Clearance. Christopher Kirman, Summit Toxicology, Bozeman, MT.

Designing QSARs for Metabolic Clearance and Plasma Protein Binding in Diverse Chemical Space Using Pharmaceutical Data. Brandall Ingle, ICF International, Research Triangle Park, NC.


Panel Discussion/Q&A.
Shifting Currents in Predictive Toxicology and Safety Evaluation with *In Vitro* and Alternative Approaches

**Tuesday, March 12, 8:00 AM to 10:45 AM**

**Chairperson(s):** Marie Fortin, Jazz Pharmaceuticals, Ewing, NJ; and Jessica LaRocca, Corteva Agriscience, Indianapolis, IN.

**Primary Endorser:** Regulatory and Safety Evaluation Specialty Section

**Other Endorser(s):** *In Vitro* and Alternative Methods Specialty Section; Molecular and Systems Biology Specialty Section

Transformative approaches, such as organotypic *in vitro* models and high content screening, are redefining the science of toxicology. However, the path to their integration in toxicity testing programs remains somewhat elusive. Toxicity testing, a necessary element of product development and the foundation of human health risk assessment, has traditionally relied heavily on *in vivo* apical endpoints. The advent of *in vitro* and computational technologies holds promise to drastically change and improve the testing paradigms of the future. Beyond the obvious benefit of reducing animal testing, embracing high-throughput predictive models can both provide valuable information to aid in molecule design and provide guidance for targeted toxicological testing strategies. This session will focus on innovative methods, such as toxicogenomics, 3D microtissues, and *in vitro* high content analysis, that are being used to characterize the safety profile of molecules and products, and their application to predictive and mechanistic toxicology testing approaches. Emphasis will be given to methods that are currently being employed to characterize the safety profile of molecules and products and inform decision-making. The targeted audience would be those interested in understanding how these tools are being leveraged in real-world applications, such as integrated approaches to testing and assessment (IATA) strategies to help prioritize and streamline chemical testing programs. To this end, experts from industry, government, academia, and non-for-profit were gathered to discuss the current state-of-the-science. The talks will present how cutting-edge research tools and next-generation alternative models are being integrated in the safety evaluation of environmental chemicals, pharmaceuticals, and plant protection products. Topics covered will include the value of *in vitro* transcriptomics to predict *in vivo* apical findings and identify point of departures; the use of a systems approach to predict and mechanistically classify kidney toxicity *in vitro*; the use of *in silico* and *in vitro* models in discovery toxicology; and the utility of 3D tissue models for screening endocrine disruptors. Following the presentations, a Q&A will be held to engage the audience. Attendees will leave with a deeper understanding of the realm of potential applications of next-generation toxicology models. They will also gain insight into the strengths, limitations, and future development opportunities of *in vitro* and alternative models for predictive toxicology.

**Introduction.** Marie Fortin, Jazz Pharmaceuticals, Ewing, NJ.

**Evaluation of *In Vivo* and *In Vitro* High-Throughput Transcriptomics for Safety Assessment.** William Gwinn, NIEHS/NTP, Research Triangle Park, NC.

**Using a Systems Approach to Predict and Mechanistically Classify Kidney Toxicity *In Vitro*.** Susanne Ramm, AstraZeneca, Boston, MA.

**Integration of *In Vitro* and *In Silico* Models for Predictive Toxicology in Discovery Molecule Development.** Jessica LaRocca, Corteva Agriscience, Indianapolis, IN.

**Screening Estrogenic Endocrine-Disrupting Chemicals with Human MCF-7 3D Microtissues by *In Vitro* Pathology.** Kim Boekelheide, Brown University, Providence, RI.

**In Vitro Hepatic Model Systems for Investigative and Predictive Toxicology Applications.** Edward LeCluyse, LifeNet Health Institute of Regenerative Medicine, Research Triangle Park, NC.

**Panel Discussion.** Marie Fortin, Jazz Pharmaceuticals, Ewing, NJ.
The World Health Organization (WHO) has estimated that indoor and outdoor air pollution causes approximately 7 million premature deaths worldwide each year, and 40,000–60,000 premature deaths in the United States alone. Implementation of the regulations of the Clean Air Act has brought forth substantial improvements in air quality and attendant benefits to public health. Yet tens of millions of Americans still live in areas where levels of air pollutants exceed US EPA’s National Ambient Air Quality Standards (NAAQS). Furthermore, some studies have shown that there is no threshold for exposure to particulate air pollution below which exposure is safe, implying that susceptible individuals may be at risk of adverse health effects not only in nonattainment areas but also in communities that are in compliance with NAAQS. Two main intervention strategies to further reducing adverse health impacts of air pollution are reducing personal exposure to air pollution and reducing vulnerability to adverse health effects of air pollution. While various intervention approaches have been proposed under each approach, it is uncertain if there is sufficient scientific basis to support their use, or if there are potential health risks associated with their use. The goal of the session is to discuss selected approaches within each of these two strategies. The session will open with a review of US EPA regulations to improve air quality and an overview of interventions aiming to reduce personal exposure to and alleviate adverse health effects of air pollution. This will be followed by five presentations on selected interventions to discuss potential benefits and risks of each strategy. Specifically, interventions focusing on reducing vulnerability to adverse cardiac and pulmonary effects of environmental pollution, such as dietary supplementations and contact with greenery, and interventions focusing on reducing exposure levels to air pollution, such as use of cleaner cookstoves in Guatemala and use of physical barriers and personal behavior changes, will be presented. The session will conclude with a panel discussion with the audience that addresses the following questions: (1) What are the top priorities to reduce the health impacts from air pollution? (2) What are strategies to reduce exposure and vulnerability to adverse health impacts of air pollution at an individual level in susceptible populations? (3) What is a preferred solution to household air pollution: better stoves or cleaner fuels? (4) What are the potential mechanisms for intervention? (5) What measures can be used to mitigate the heath impact of air pollution at the community level? (6) What other nontraditional approaches can be used to mitigate the health impact of environmental pollutants? Following this session, attendees will have a better understanding of the research needs and opportunities to deploy such approaches to mitigate damage from air pollutants.

**Better Stoves or Cleaner Fuels: What Is the Evidence Base That Is Needed to Decrease the Burden of Household Air Pollution?**
John Balmes, University of California Berkeley, Berkeley, CA, and University of California San Francisco, San Francisco, CA.

**Vitamin E (Gamma-Tocopherol)-Based Intervention for Environmental Airway Disease.**
Neil Alexis, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Dietary Intervventional Approach to Ameliorate the Health Effects of Air Pollution.**
James Samet, US EPA, Research Triangle Park, NC.

**Personal Solutions to Air Pollution: What Does the Evidence Recommend?**
Howard Kipen, Rutgers, The State University of New Jersey, Piscataway, NJ.

**Urban Green Spaces Reduce Stress-Related Allostatic Load and Enhance Resilience to Environmental Insults.**
Andrey Egorov, US EPA, Chapel Hill, NC.

**Panel Discussion/Q&A.**
The Delaney Clause, from 1958 to 2019: Making the Model Relevant

**Tuesday, March 12, 11:00 AM to 12:20 PM**

**Chairperson(s):** Lisa Navarro, Givaudan Flavors, Cincinnati, OH; and Mansi Krishan, Danone North America, Louisville, CO.

**Primary Endorser: Food Safety Specialty Section**

**Other Endorser(s):** Association of Scientists of Indian Origin Special Interest Group; Regulatory and Safety Evaluation Specialty Section

The Delaney Clause of the Federal Food, Drug, and Cosmetic Act, named after Congressman Jim Delaney, was enacted in 1958 because he was worried that potential harmful chemicals were finding their way into foods and were responsible for causing cancer. It states that “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.” The US FDA and US EPA are the two federal agencies charged with implementing this clause. It has been 60 years and significant advances in cancer research have elucidated the causes and mechanisms by which chemicals induce cancer. Advancements in analytical methodologies are allowing for accurate and progressively lower detection limits, resulting in detection of trace amounts of chemicals. Based on the current scientific knowledge, there is a need to look at the Delaney Clause from a different lens and make it more relevant. As a scientific community, we are committed to improving public health by promoting the development and utilization of appropriate and relevant science in risk assessment and regulatory decision-making. The objective of this roundtable session is to provide a balanced discussion and propose a path forward. The presenters in the session will provide (1) a historical overview of the scientific advances in cancer research since the 1950s, (2) the role of the Delaney Clause in the current regulatory paradigm, (3) a case study demonstrating the impact of the Delaney Clause on scientific advances, and (4) a proposed path forward on the Delaney Clause to make it more relevant based on 21st-century science.

**Session Overview.** Lisa Navarro, Givaudan Flavors, Cincinnati, OH.

**Updating the Delaney Clause: Mode-of-Action Considerations for Carcinogens.** Barbara Beck, Gradient, Boston, MA.


**Pro-Delaney Perspective.** Michael Dourson, TERA, Cincinnati, OH.

**Developing a Path Forward to Make the Delaney Clause More Relevant Based on Current Science.** Ricardo Carvajal, Hyman, Phelps & McNamara, P.C., Washington, DC.

**Moderated Panel Discussion.** Mansi Krishan, Danone North America, Louisville, CO.

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**Past Presidents’ 5K Fun Run/Walk**

**March 12, 2019**

Camden Yards Sports Complex
Baltimore, Maryland

Register at www.toxicology.org/funrun
Challenges and Opportunities Encountered with TSCA Reform: Working toward a Shared Vision for Product Safety

Tuesday, March 12, 11:00 AM to 12:20 PM

Chairperson(s): Darrell Boverhof, Dow Chemical Company, Midland, MI; and Jeffery Morris, US EPA, Washington, DC.

Primary Endorser: Risk Assessment Specialty Section

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section

The Lautenberg Chemical Safety Act (LCSA) was signed into law in June of 2016 to reform the Toxic Substances Control Act (TSCA). Its requirements provide many opportunities for improvements in how the science and information concerning the manufacture and use of chemicals are applied for ensuring safety regarding chemical exposures. While the scope covers many issues, the primary focus has been on how the US EPA will carry out its mandate to evaluate both new and existing chemicals and manage those that pose an unreasonable risk. Specifically, US EPA has been working on updating the pre-manufacture notification (PMN) process covered in Section 5, as well as developing processes to prioritize and evaluate existing chemicals in commerce under Section 6, in accordance with new science standards laid out in Section 26. Since the law became effective upon enactment, US EPA has been required to meet many statutory deadlines in a short timeframe (e.g., finalize the prioritization and risk evaluation rules, complete scoping documents on the initial 10 chemicals selected for risk evaluation). In addition, the PMN process has been undergoing “fixes” in real time as attempts are made to navigate the statutory requirements for new chemicals without undue delays hindering innovation. More recently, discussions about data transparency for information used by US EPA in its regulatory decisions have become a prominent part of the narrative. In addition, there are extensive efforts around how nonanimal approaches can be used to fill data and information needs. There are both challenges and opportunities that must be addressed. Each of the three presentations will provide the perspective of the groups they represent on how these challenges and opportunities can be addressed to achieve progress toward an improved chemicals management process in the US.

Introduction. Darrell Boverhof, Dow Chemical Company, Midland, MI.


Perspectives on TSCA Implementation. Michael Walls, American Chemistry Council, Washington, DC.

TSCA Implementation: A Focus on New Approach Methodologies. Kristie Sullivan, Physicians Committee for Responsible Medicine, Washington, DC.

Panel Discussion/Q&A.
Wildfires are increasing in frequency, size, and intensity in the United States, resulting in significant impacts to air quality locally, regionally, and nationally as smoke is transported across the country. Smoke from wildland fires, which include prescribed burns, now accounts for up to 40% of the fine particulate matter (PM2.5) in the country, affecting the ability of some states to meet the National Ambient Air Quality Standards. Emissions from fires also contribute to the formation of ozone and other pollutants that impact public health. Smoke plumes can extend for hundreds of miles across state and national boundaries, making any given wildfire, and a season of wildfire events, a national community health issue. The potential health effects from exposure to wildland fires require a more thorough investigation to address this growing health threat. Toxicological, epidemiological, and clinical-based research is providing new insights into the health impacts of smoke from fires and how to protect exposed populations. Research is improving understanding of who is most vulnerable and at greater risk from smoke events, and identifying health outcomes in these populations. Health studies are informing investigations to enhance public health intervention strategies and communications before, during, and after a fire. This session provides an overview of the impact wildfires and prescribed burns are having on air quality and the state of knowledge about the health effects from smoke events. The session will describe research to improve understanding of smoke toxicity, highlight clinical-based findings and describe innovative approaches to communicating the health risks.


Clinical Symptoms Associated with Wildfire Smoke Exposure. Joseph Domitrovich, US Forest Service, Missoula, MT.

Long-Term Health Outcomes of Early-Life Wildfire Smoke Exposure in a Nonhuman Primate Cohort. Lisa Miller, University of California Davis, Davis, CA.

Nonalcoholic fatty liver disease (NAFLD) is a progressive disease recognized as the underlying liver pathology associated with obesity and metabolic syndrome. Poor diet and lifestyle are implicated as pathogenic factors in the development and progression of NAFLD, with emerging evidence implicating exposures to environmental contaminants in the initiation, perturbation, and/or acceleration of NAFLD progression. Accumulating molecular toxicology data suggest that environmental contaminants target mechanisms associated with NAFLD progression to induce and/or enhance steatosis, inflammation, and fibrosis, and increase risk for more complex metabolic diseases, including metabolic syndrome, diabetes, cardiovascular disease, and hepatocellular carcinoma. Moreover, NAFLD is emerging as the second leading cause of liver transplantation. The complexities related to NAFLD progression, the stage of disease when environmental exposures occur, and the specific pathways affected have confounded the delineation of risk and limited the development of effective treatment options. The goals of this session are to (1) explicate recent advances in the elucidation of NAFLD progression mechanisms, and (2) build a consensus regarding future research into the role of environmental contaminants in NAFLD development and progression. To achieve these goals, experts in this field will present recent data and address future challenges. Questions that will be addressed include: How do hepatotoxic compounds that drive NAFLD progression affect pathophysiological factors associated with each stage of NAFLD? Can NAFLD and toxicant-associated fatty liver disease (TAFLD) be distinguished when exposure is variable across a lifetime and/or in the presence of obesity and metabolic syndrome? What are the potential biomarkers that will help with delineation of TAFLD from NAFLD? How do external factors such as diet influence exposure to and the toxicity of compounds that drive NAFLD progression? Are there additional adverse outcome pathways that can be developed for each stage of NAFLD? This session will include novel data for the roles of per- and polyfluoroalkyl substances, the mechanistic role of aryl hydrocarbon receptor, and the importance of hepatocyte defenses in NAFLD development and progression. In addition, this session will include novel biomarker data designed to circumvent the limitations of standard liver toxicity biomarkers and invasive diagnostic techniques. Session attendees will gain a greater appreciation of the role of environmental factors in NAFLD progression and a more comprehensive understanding of key factors involved in the progression of NAFLD. Taken together, information from this session has implications for risk assessment in affected populations and for defining mechanisms and potential biomarkers of liver damage.

**Differing Effects of Perfluorooctanesulfonic Acid-Induced Hepatic Steatosis: Influence of Diet Type and Timing for Hepatic Steatosis Outcomes.** Angela Slitt, University of Rhode Island, Kingston, RI.

**The Progression of Steatosis to Steatohepatitis with Fibrosis following Aryl Hydrocarbon Receptor (AhR) Activation.** Timothy Zacharewski, Michigan State University, East Lansing, MI.

**Toxicant-Associated Steatohepatitis: Clinical and Translational Studies.** Matthew Cave, University of Louisville, Louisville, KY.
Integrated ‘Omics Approaches to Toxicity Assessments

Tuesday, March 12, 1:00 PM to 2:30 PM

Chairperson(s): Julia Rager, University of North Carolina at Chapel Hill, Chapel Hill, NC; and Scott Auerbach, NIEHS/NTP, Research Triangle Park, NC.

Primary Endorser: Biological Modeling Specialty Section

Other Endorser(s): Molecular and Systems Biology Specialty Section; Risk Assessment Specialty Section

Recent advances surrounding assay and sequencing-based technologies have increased the feasibility of multi-‘omics research, wherein two or more ‘omic profiles (e.g., genomics, transcriptomics, epigenomics, metabolomics, and proteomics) are integrated and evaluated to further understand molecular mediators of biological function and cellular health. Multi-‘omic analysis strategies rely upon the joint analysis of multiple data types, yielding toxicity responses that may not have been identified given the analysis of only one ‘omic endpoint. Integrated analyses provide insights into how the features of the ‘omics interact through biological networks, resulting in an integrated systems level understanding of toxicity. The utilization of multi-‘omic strategies presents the opportunity to elucidate hierarchical processes in complex systems that can further substantiate mechanisms of action linking chemical exposures to disease, which ultimately aids in the accurate assessment of chemical risk and overall protection of public health. Integrated ‘omics strategies are also employed to understand mechanisms of action linking pharmaceuticals to health outcomes. However, methods and associated databases that can be leveraged to integrate multi-‘omic response signatures that result in findings useful for drug development and chemical assessments are still under development, with current limitations that require further research. This session will address this growing research area by discussing multi-‘omic data integration tools, data reduction methods, dose-response modeling, toxicity predictions based on machine learning algorithms, and systems level analyses to elucidate molecular pathways involved in disease etiology. Case studies also will be discussed to provide examples of how multi-‘omic response signatures can inform toxicity assessments relevant to environmental regulation and the chemical/pharmaceutical industries.

Introduction. Julia Rager, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Computational Tools for Multi-‘Omics Integration. Karan Uppal, Emory University, Atlanta, GA.

An Integrated ‘Omics Dose-Response Assessment from Short-Term In Vivo Studies of the Two Aromatics Phosphate Flame Retardants. Scott Auerbach, NIEHS/NTP, Research Triangle Park, NC.

On-the-Fly Machine Learning to Predict Adverse Drug Reactions by ‘Omics Integration of Drug Properties. Avi Ma’ayan, Icahn School of Medicine at Mount Sinai, New York, NY.

Scientific and Regulatory Update in the Application of the 3Rs Principle in Chemical and Drug Development

Tuesday, March 12, 1:00 PM to 2:30 PM

Chairperson(s): A. Wallace Hayes, University of South Florida, Tampa, FL; and Brinda Mahadevan, Abbott Laboratories, Mumbai, India.

Primary Endorser: Ethical, Legal, Forensics, and Societal Issues Specialty Section

Other Endorser(s): In Vitro and Alternative Methods Specialty Section; Regulatory and Safety Evaluation Specialty Section

The 3Rs principle (3Rs), developed as a framework for humane research, has become embedded in animal use legislation. There remains ample opportunity to improve efficient usage of animals and to facilitate the 3Rs, with the availability of new in vitro/in silico technologies. Most toxicology studies are conducted to determine safe doses and a reasonable margin of safety. This facet is considered during pharmaceutical development. In case of nonproprietary pharmaceuticals wherein the toxicity of the active is known and the excipients are
not novel or adhere to regulatory guidelines, the need to conduct in vivo studies is minimal. However, country regulatory requirements vary and repeat of studies may be necessary. At the global level, although there are ongoing discussions on the 3Rs, follow-up and implementation have not been rapid and many countries have a lot of catching up to do, especially in revamping their country regulation. This symposium session will address the following objectives: (1) to understand the need to conduct animal studies to address safety/efficacy and meet regulatory requirements for nonproprietary pharmaceuticals; (2) to adopt in vitro, in chemico, and in silico approaches for skin sensitization; and (3) to comprehend human-relevant, nonanimal methodologies to predict toxicity and provide a scientific underpinning for the use of read-across techniques.

3Rs in the Development of Nonproprietary Pharmaceuticals. Brinda Mahadevan, Abbott Laboratories, Mumbai, India.


Novel Strategies for the Implementation of 3Rs: Case Studies on What Has Worked Best in Europe. Marcel Leist, University of Konstanz, Konstanz, Germany.

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**Adverse or Not Adverse? Thinking Process behind Adversity Determination during Nonclinical Drug Development**

**Tuesday, March 12, 1:00 PM to 2:30 PM**

**Chairperson(s):** Vijaykumar Kale, Battelle Memorial Institute, Columbus, OH; and Lawrence Thomas, Celldex Therapeutics Inc., Needham, MA.

**Primary Endorser: Drug Discovery Toxicology Specialty Section**

**Other Endorser(s):** Association of Scientists of Indian Origin Special Interest Group; Biotechnology Specialty Section

The determination of adversity, and a No-Observed-Adverse-Effect-Level (NOAEL), is often a fundamental component of the analysis of toxicological data. A NOAEL is often the basis for the determination of the First-In-Human (FIH) dose, although alternative methodologies like Highest Non-Severely Toxic Dose (HNSTD) and Minimum Anticipated Biological Effect Level (MABEL) have emerged to address specific situations. While the definition of adversity has often been a judgment call based on experience, a number of organizations have undertaken efforts to streamline and standardize the definitions and guidance on how to determine adversity. Study directors, pathologists, safety pharmacologists, preclinical drug development leads, and regulatory reviewers are among the key players involved in safety assessment who may have different perspectives and sometimes disagreements about determining adversity. The purpose of the session is to discuss the current thinking process behind the determination of adversity in nonclinical toxicology studies from multiple points of view. Moreover, all the speakers also will discuss their perspectives about dealing with unique situations in a toxicology study such as nonlinear vs. linear kinetics, sex differences in toxicokinetics and observed toxicity, (mis)use of historical control data, No-to-Partial Recovery of toxic effects, and on-target vs. off-target effects. Presenters will discuss these scenarios with the help of case studies wherever possible.

- **Introduction.** Vijaykumar Kale, Battelle Memorial Institute, Columbus, OH.
- **Determining Adversity and NOAEL: A Study Director's Perspective.** John Kapeghian, Preclinical Safety Associates, LLC, Reno, NV.
- **A Pathologist's Perspective on Determining Adversities in Nonclinical Toxicology Studies of Therapeutics.** Bhanu Singh, Janssen Research & Development, Spring House, PA.
- **A Regulatory Perspective of Determining Adversity and Translating Findings from Nonclinical Studies.** Ilona Bebenek, US FDA, Silver Spring, MD.
- **Panel Discussion/Q&A.**

**Assessing the Bisphenol Class of Chemicals**

**Tuesday, March 12, 1:00 PM to 2:30 PM**

**Chairperson(s):** John Szilagyi, Rutgers, The State University of New Jersey, Piscataway, NJ; and Vicki Sutherland, NIEHS/NTP, Research Triangle Park, NC.

**Primary Endorser: Reproductive and Developmental Toxicology Specialty Section**

**Other Endorser(s):** In Vitro and Alternative Methods Specialty Section; Regulatory and Safety Evaluation Specialty Section

The bisphenol class of chemicals includes over 20 analogues that have different structural, chemical, and biological activities. The primary analogue of interest in this class is Bisphenol A (BPA), a chemical widely utilized in plastics, epoxy resins, and other products. Most of the other analogues are not routinely used or used at high production levels, but exposure to some has led to evaluations to determine
if there is any toxicological evidence for concern. The complications associated with toxicological evaluation of BPA may be attributed
to the ubiquitous nature of this chemical. Carefully assessing the effects of this compound in animal studies is extremely difficult due
to the requirement to control and monitor BPA from all external sources. It has therefore become essential to characterize dosing solu-
tions, housing materials, and internal dose measurements to ensure that the animals are exposed to the levels of the chemical that the
protocol dictates. While the analogues may not generate such a high level of attention, the primary question regarding their potential
risks to humans is exposure levels. BPA is currently found at levels far exceeding any other analogue and its unique nature ensures that
it is not easily replaced in a majority of products; however, there is evidence that the analogues are in use and information on their
potential effects and endocrine activity will be essential if their use increases. An additional concern associated with assessing classes of
compounds is determining effective methods to quickly and efficiently evaluate multiple analogues. High-throughput screening data
and in vitro assays are not reliably “predicting” in vivo outcomes. This may be due to the use of assays not applicable for this class, focusing
assessments to just the estrogen and androgen receptors, limitations with in vitro metabolism, or not recognizing that there needs to
be a compromise when evaluating chemicals that are potential endocrine activators. Therefore, how to best generate reproducible and
reliable data and understand the biology and/or chemistry of conflicts as they arise, as well as collecting routine internal measurements
of the compound(s), may need to be a primary focus for those assessing chemicals in this group. The session will begin with an overview
of the bisphenol class of chemicals and highlight its uses and products and then discuss testing of select analogues before discussing
limitations of the in vitro assessments for this class of chemicals. In summary, the session will provide an overview of the bisphenol class
of chemicals and the data that we have to date on the analogues, and discuss best methods for evaluating these compounds and the next
steps in the assessment process. (This overview does not necessarily reflect any Agency opinion.)

Introduction. John Szilagyi, Rutgers, The State University of New Jersey, Piscataway, NJ.
The Bisphenol Class of Chemicals: Uses, Analogues, and Importance. Evelyn Majoris, Covestro, Pittsburgh, PA.
In Vivo Comparisons of Bisphenol A (BPA), Bisphenol AF (BPAF), and Bisphenol S (BPS). Vicki Sutherland, NIEHS/NTP,
Research Triangle Park, NC.
Estrogenicity and Antiandrogenicity of Bisphenols: Uncertainties in Extrapolating from In Vitro Molecular Initiating Events (MIE)
and In Vivo Key Events (KE) to Adverse Reproductive Outcomes. L. Earl Gray, US EPA/ORD, Research Triangle Park, NC.
Panel Discussion/Q&A.

In Vitro Static and Dynamic Skin Metabolism Methods and Strategies to Address
the Safety Assessment of Topically Applied Chemicals
Tuesday, March 12, 1:00 PM to 2:30 PM
Chairperson(s): Andreas Schepky, Beiersdorf AG, Hamburg, Germany; and Sandra Coecke, EURL ECVAM, Ispra, Italy.
Primary Endorser: Dermal Toxicology Specialty Section
Other Endorser(s): In Vitro and Alternative Methods Specialty Section; Molecular and Systems Biology
Specialty Section

Understanding a chemical’s bioavailability, either locally or systemically, is important for predicting adverse effects and conducting a
safety assessment. Metabolism was originally thought to be an inactivation or detoxification pathway for xenobiotics; however, today
it is generally accepted that metabolism-mediated toxicity is important in regulatory toxicity. Therefore, all in vitro toxicity methods
proposed for regulatory risk assessment should include careful consideration of metabolism-mediated toxicity. In addition to a detailed
knowledge on metabolism, the biokinetics of the test chemicals in the in vitro method setup will be vital for designing the most valuable
and predictive integrated test strategies. The main exposure route of cosmetic ingredients is via the skin. However, once the parent
compound or metabolites formed in the skin enter the systemic circulation, they can be further metabolized systemically (e.g., by the
liver). In vivo skin models can help to predict the amount of parent and metabolite(s) formed locally in the skin and escaping first pass
skin metabolism. The session will present examples of metabolism of relevant chemicals in ex vivo human skin explants compared to S9
fractions from EpiSkin. Incubations with human liver S9 were also included to allow a comparison of dermal and hepatic metabolism. An
additional consideration is how the frequency and route of application of a chemical and its interaction with different organs can affect
the kinetics and ratio of different metabolites formed systemically. For example, first pass skin effects have been reported for aromatic
hair dyes as well as for several topically applied glucocorticoids. The route of exposure (topical vs. systemic application) may differentially determine a chemical’s effect on the liver. Qualitative as well as quantitative differences may be important aspects for risk assessment in cosmetic risk assessment. The session will present how a 3D skin-liver dynamic model can help us understand the interaction between skin and liver metabolism over extended and repeated exposure of a test chemical via different routes (topical vs. systemic) and how it affects systemic concentrations of both parent chemical and its metabolites. The threshold of toxicological concern (TTC) is a safety assessment tool that involves establishing a low-level exposure value, from known chemicals with curated toxicity data, below which there is a low probability of adverse effects for chemicals lacking sufficient safety data. The TTC concept has evolved over the last 50 years and a logical next step in the continued evolution of TTC is to develop this concept further by converting the external NOAEL values to internal concentrations. This is especially relevant for chemicals with a low absorption, either via the oral or dermal routes, and thus relevant to the cosmetics, pharmaceutical, and chemistry industries. The development of iTTC thresholds would provide conservative hazard-based values that could be utilized in exposure-based safety assessments in the context of (1) refinement of de minimis exposure levels for dermal exposures, (2) metabolism-based structure-activity relationship (SAR) assessments, (3) low-level aggregate exposures from different dose routes, or (4) in vitro biological assays. The session will provide an update on the development of iTTCs and present case study examples for possible uses. In the absence of the use of animal studies in the cosmetics industry for safety assessment, in vitro alternatives and strategies to waive additional tests (e.g., the iTTC) are essential.

**Introduction.** Andreas Schepky, Beiersdorf AG, Hamburg, Germany.

**Studying In Vitro Metabolism of Cosmetics Ingredients in Skin Explants or by Using Liver- or Skin-Derived S9 Sub-Cellular Fractions.** Carine Jacques Jamin, Pierre Fabre Dermo-Cosmétique, Toulouse, France.

**Understanding Chemical Metabolism in Skin and Liver Models over Extended and Repeated Exposure in a Multi-Organ Chip Device.** Jochen Kuehnle, Beiersdorf AG, Hamburg, Germany.

**Internal Thresholds of Toxicological Concern as Tools for Assessment of Exposures via Oral and Dermal Routes.** Corie Ellison, Procter & Gamble Company, Cincinnati, OH.

**Panel Discussion/Q&A.**

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**Innovation in Biomarker Qualification**

**Tuesday, March 12, 1:00 PM to 2:30 PM**

**Chairperson(s):** Shashi Ramaiah, Pfizer, Inc., Cambridge, MA; and John-Michael Sauer, Critical Path Institute, Tucson, AZ.

**Primary Endorser: Clinical and Translational Toxicology Specialty Section**

Biomarkers have become highly utilized tools in the drug development process. However, the unknown regulatory acceptance of biomarker data has made the routine incorporation of these tools and interpretation of their data unclear for some companies. Qualification of biomarkers removes this uncertainty for drug developers. This session will provide attendees with an overview of the US FDA Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP) under the 21st Century Cures Act. US FDA BQP works with external stakeholders to develop biomarkers as drug development tools (DDT) to provide regulatory certainty regarding the acceptance of these tools. Presenters will discuss how the Critical Path Institute (C-Path), through their Predictive Safety Testing Consortium (PSTC), is working to advance qualification of novel safety biomarkers. Further, the newly formed TransBioLine (Translational Biomarker Pipeline) consortium of EFPIA pharmaceutical companies and leading European academic institutions and bioanalytical companies, which has been established to build on previous consortia work to advance regulatory qualification of new and emerging safety biomarkers, will be presented.

**21st-Century Cures Biomarker Qualification Program.** Christopher Leptak, US FDA, White Oak, MD.


**Panel Discussion/Q&A.**
Microbiota and Contributions to Neurodevelopment: Implications in Neurological Function, Behavior, and Toxicity

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Troy Hubbard, NIEHS/NTP, Research Triangle Park, NC; and Charlene McQueen, University of Arizona, Tucson, AZ.

Primary Endorser: Neurotoxicology Specialty Section

Other Endorser(s): Molecular and Systems Biology Specialty Section; Reproductive and Developmental Toxicology Specialty Section

The host and its associated microbiome evolved as a cooperative unit that influences multi-factorial host physiological and pathological outcomes. Disruption of host-microbial mutualism is associated with numerous effects upon metabolism, immune function, and organogenesis. For example, sensitive periods of brain development and formation of neural circuitry are influenced by both intrinsic and extrinsic signals, including maturation of the gastrointestinal microbiome. While a connection between gut microbiota and the brain may seem unlikely, emerging data support the concept of the microbiota-gut-brain axis. Alterations in gut microbiota are associated with decreased social behavior, increased stress response, hyperactivity, reduced anxiety, and deficits in learning and memory. These findings implicate the microbiome as an omnipresent environmental factor that influences brain development, directly impacting functions of memory, behavior, personality, and higher cognition. The session contains presentations by both academic and government scientists to introduce concepts on the role of physiologic perturbations or toxic insults to the gut microbiome and its implications in neurodevelopment using both human and animal models. The first speaker illustrates how human microbial colonization at birth and life-stage transitions of the microbiome have implications in later cognitive function. A proposed mechanism for communication between gut microbes and the developing brain is presented next. Using conventional and germ-free mice, microbial signaling molecules capable of influencing host brain development and behavior have been identified. The final presentation utilizes a zebrafish model to investigate host-associated microbiota capacity to modify developmental neurotoxicity of environmental chemicals. Overall, these presentations will provide a better understanding of the function of the microbiota-gut-brain axis in neurodevelopment and the potential consequences of chemical exposures.

Introduction. Troy Hubbard, NIEHS/NTP, Research Triangle Park, NC.

Characterizing the Microbiome-Gut-Brain Axis in Human Infants. Rebecca Knickmeyer, University of North Carolina School of Medicine, Chapel Hill, NC.

Bacterial Peptidoglycans as Novel Signaling Molecules from Microbiota to Brain. Rochellys Diaz Heijtz, Karolinska Instutet, Solna, Sweden.

Examining Microbiota as a Modifying Factor for Developmental Neurotoxicity. Tamara Tal, US EPA/NHEERL, Research Triangle Park, NC.

Novel Safety Biomarker Qualification: Updates and Progress

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Alison Harrill, NIEHS/NTP, Research Triangle Park, NC; and Jennifer Burkey, Critical Path Institute, Tucson, AZ.

Primary Endorser: Clinical and Translational Toxicology Specialty Section

The Critical Path Institute’s Predictive Safety Testing Consortium (PSTC) has been working on regulatory endorsement of translational safety biomarkers for a number of target organ toxicities. Working groups within PSTC have been established focusing on liver, kidney,
skeletal muscle, vascular, pancreas, and testes, identifying and evaluating novel safety biomarkers that outperform conventional biomarkers of toxicity for these tissues. This symposium will focus on working group updates for kidney, pancreas, and vascular injury biomarkers. Each presentation will provide an overview of the progress within each working group, including the clinical qualification efforts for the kidney injury working group, the early transition to the clinic for the vascular injury working group, and the early identification of novel pancreatic injury biomarkers in preclinical species to inform future translational work. The presentations will provide an overview of the biomarkers under evaluation, proof of concept data (both preclinical and clinical), and the status of regulatory engagement seeking formal qualification. Discussion will also include recent interactions with the Innovative Medicines Initiative (IMI) TransBioLine project, which will focus on clinical qualification efforts for biomarkers for each target tissue, building on the work of PSTC.

**Drug-Induced Kidney Injury Clinical Biomarkers.** Frank Sistare, Merck & Co., West Point, PA.

**Pancreatic Injury Biomarkers.** Michael Ringenberg, GlaxoSmithKline, plc, King of Prussia, PA.

**Current Approach to Vascular Injury Safety Biomarkers, Use of Surrogate Patient Populations, Animal Models, and Novel Bioimaging Endpoints.** Robert Johnson, Novartis, East Hanover, NJ.

### Perfluoroalkyl Substances (PFAS): Global and Persistent Environmental Contaminants

**Tuesday, March 12, 3:00 PM to 4:30 PM**

**Chairperson(s):** Melanie Abongwa, Iowa State University, Ames, IA; and Lauren Walker, University of California Riverside, Riverside, CA.

**Primary Endorser: Postdoctoral Assembly**

**Other Endorser(s):** Graduate Student Leadership Committee; Mechanisms Specialty Section

Perfluoroalkyl substances (PFAS) are a diverse group of chemicals that have been used in the production of industrial and consumer products worldwide since the 1950s. Structurally, PFAS have a characteristic hydrophobic alkylated chain that is saturated with fluorine atoms attached to a hydrophilic head. Their hydrophobic and hydrophilic properties make PFAS suitable for manufacturing of a variety of products, including nonstick cookware, liquid repellants, fire-fighting foams, protective coatings, additives, textiles, and leather and carpet goods. The two most extensively studied PFAS are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Although no longer manufactured in the United States, PFOA and PFOS are still used in the manufacturing of consumer products in other countries that can be imported into the country. Consequently, most people have been exposed to PFOA and PFOS unknowingly, as they tend to end up in the environment (air, water, soil, etc.). In addition, PFOA and PFOS are known to be persistent, bioaccumulative, and toxic (PBT) in animals and humans. Studies have shown that they can cause immunological, reproductive, and developmental toxicity in experimental animals, as well as liver and kidney damage. Exposure to both chemicals has also been linked to the formation of cancerous tumors in animals. There is evidence that humans exposed to PFOA and PFOS can develop increased cholesterol levels, thyroid hormone disruption, and cancer. The goal of this session is to bring together graduate students and postdoctoral scientists from different sectors to address the emerging scientific, environmental health, and regulatory issues raised by PFOA and PFOS. The first speaker will present on the use of various zebrafish assays to assess developmental neurotoxicity following PFOA and PFOS exposure. The second speaker will discuss the potential mechanisms by which PFOA and PFOS cause fetal growth restriction in mice. Finally, the last speaker will talk about the modulatory effects of PFOA and PFOS on GABAA receptor function and neuronal network activity in primary rat cortical neurons.

**Introduction.** Melanie Abongwa, Iowa State University, Ames, IA.

**Exposure to PFO, PFHpS, PFHxS, or PFHxA Elicits Developmental Neurotoxicity in Larval Zebrafish.** Shaza Gaballah, US EPA/ORISE, Durham, NC.

**An In Vitro Screen of a Panel of Perfluoroalkyl Substances and an In Vivo Assessment of Effects on Placental and Fetal Growth.** Bevin Blake, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) Differentially Modulate GABAA Receptor Function and Spontaneous Neuronal Network Activity.** Anke Tukker, Utrecht University, Utrecht, Netherlands.
Species Relevance: Approaches to Determine the Most Relevant Species for Safety Assessment of Pharmaceutical Products

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Marcus Delatte, US FDA/CDER, Silver Spring, MD; and Simon Authier, Citoxlab North America, Laval, QC, Canada.

Primary Endorser: Comparative and Veterinary Specialty Section

Most development programs for pharmaceutical products employ a rodent and nonrodent species for assessment of potential hazards. In a risk assessment, findings from the most relevant species are typically used to determine safe clinical exposure levels. Many scientists typically conclude that the most sensitive species is the most relevant species. However, there are instances in which the most relevant species may be selected based on anatomy, physiology, target site for efficacy, pharmacokinetic profile, or other relevant factors. Identifying the most relevant species is a critical step in hazard/risk assessment given the need to determine that the hazards identified are clinically relevant and representative of effects likely to occur in humans, based on qualitative and quantitative aspects of the hazard(s) identified. This session provides attendees with an overview of factors used to determine the most relevant species for product evaluation, an examination of case studies used to illustrate the challenges encountered when determining the most relevant species, and a discussion of practical approaches employed to evaluate the clinical relevance and utility of hazards identified. The first talk will introduce the attendees to multiple factors that may impact species relevance when conducting a hazard assessment. The second talk will discuss risk assessment of small molecules and approaches used to determine the most relevant species in pharmacology and general toxicology studies. The third talk will discuss approaches used to determine the most relevant rodent species for carcinogenicity assessment of small molecules. The fourth presentation will discuss hazard assessment of biologic products and approaches used to determine the most relevant species for reproductive toxicology studies and carcinogenicity assessment. Together, the information presented in these talks will highlight the importance of and provide a framework for selecting the most relevant species when conducting a safety assessment.

Comparative Anatomy and Physiology in Animal Species Commonly Used for Drug Safety Testing. James Turk, Amgen, St. Louis, MO.

Species Selection in Toxicology and Pharmacology Studies: Challenges, Opportunities, and Lessons Learned. Simon Authier, Citoxlab North America, Laval, QC, Canada.

Species Considerations for Nonclinical Carcinogenicity Evaluations. Owen McMaster, US FDA, Silver Spring, MD.


Panel Discussion/Q&A.

The Current Application, Limitations, and Recent Advances in Humanized Mouse Models for Evaluations of Immune Function and Preclinical Immunotoxicology Studies

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Mark Collinge, Pfizer, Inc., Groton, CT; and Michael Brehm, University of Massachusetts Medical School, Worcester, MA.

Primary Endorser: Immunotoxicology Specialty Section

Significant advances have been made in recent years in the development of humanized mice for use in preclinical pharmacology and toxicology studies to support the development of pharmaceutical biotherapeutics. Multiple models currently exist, and the selection of the appropriate model is critical to provide meaningful and clinically translatable data. This session will provide an overview of current models, including details regarding the engraftment of specific immune cell subsets, and their potential application. The limitations of each of these models also will be discussed. Examples of current applications will be discussed, including assessment of their value in...
evaluating cytokine release, graft-versus-host disease, and comparative assessments of biosimilar products. Recent advances in humanized mouse models will be presented including novel, rapid, and sensitive in vivo models to assess individual responses to immune therapy agents and in combination therapies.

**NSG Mice Deficient in Murine MHC Class I and Class II Expression Support Engraftment of Functional Human T Cells in the Absence of Acute Xenogeneic GVHD following Injection of PBMC.** Michael Brehm, University of Massachusetts Medical School, Worcester, MA.


**Recent Advances in the Utilization of Humanized Mouse Models for Toxicology Assessment of Novel Therapeutics.** James Keck, The Jackson Laboratory, Sacramento, CA.

**When "Natural" Is Not Synonymous with "Safe": Toxicity of Natural Products Alone and in Combination with Pharmaceutical Agents**

*Tuesday, March 12, 3:00 PM to 4:30 PM*

**Chairperson(s):** Donna Mendrick, US FDA/NCTR, Silver Spring, MD; and Cathy Yeung, University of Washington, Seattle, WA.

**Primary Endorser: Scientific Liaison Coalition**

**Other Endorser(s):** Clinical and Translational Toxicology Specialty Section; Regulatory and Safety Evaluation Specialty Section

Retail sales of vitamins and nutritional supplements have increased from $23.8 billion in 2007 to $36.1 billion in 2017, with more than 70% of Americans currently taking some dietary supplement daily. While many equate these “natural” products with “safe,” it is well recognized by scientists that active ingredients in natural products can result in toxicity. Additionally, when these products are used in concert with pharmaceutical agents, they can alter drug metabolism and drug delivery, thereby enhancing or reducing the therapeutic effect of the drug(s). However, there is no current requirement for dietary supplements to be registered with the US FDA, and only post-marketing adverse events have to be reported. With the widespread use of nutritional supplements, these dietary supplement-drug interactions can be underappreciated and cause the failure of promising drugs. This symposium will explore the toxicity of natural products alone and in combination with conventional drugs. Systematic approaches for assessing natural product-drug interactions, including in vitro, PBPK modeling, and human clinical studies, will be presented. Methodology to handle the complex mixtures represented by natural products in various test systems also will be discussed. Finally, a case study involving a natural product (cannabidiol) and potential for drug interaction will be highlighted.

**Introduction.** Donna Mendrick, US FDA/NCTR, Silver Spring, MD.

**Causative Ingredients and Mechanisms Underlying Interactions between Prescription and Nonprescription Medications and Natural Products.** Mary Paine, Washington State University, Spokane, WA.


**Cannabidiol Pharmacology and Drug-Drug Interactions with Anti-Epileptic Drugs (AEDs).** Tyler Gaston, University of Alabama at Birmingham, Birmingham, AL.

**Closing Remarks.** Cathy Yeung, University of Washington, Seattle, WA.
New Approaches Using Mode-of-Action to Predict Acute and Systemic Toxicity

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Catherine Willett, Humane Society of the United States, Washington, DC; and Daniel Wilson, Dow Chemical Company, Midland, MI.

Primary Endorser: Scientific Program Committee

There is a transformation occurring in toxicology: a shift toward characterizing chemical safety based on an understanding of the biomolecular activity of the chemical coupled with a deeper understanding of how that activity can lead to adverse effects at the organ, individual, or population level. New approach methodologies (NAMs) can be used to identify a chemical's mode of action (MoA), including the molecular initiating events (MIEs) and downstream key events possibly leading to adverse outcomes (AOs). Application of this NAM paradigm is furthest advanced for biology where the MIEs are better established, such as skin sensitization, genetic toxicity, and endocrine models. However, for systemic acute or repeat-dose toxicity, where several possible MIEs may be involved, the ability to identify specific MIEs and use in vitro data to predict complex toxicological outcomes is much less mature and urgently needed. This session provides three innovative approaches to predicting chemical safety by identification of MoA based on NAM data: one for acute mammalian systemic toxicity, and two different approaches for repeat-dose target organ toxicity. The presentations will provide a synopsis of the state-of-the-science regarding availability of databases for these endpoints, as well as application of integrating computational and in vitro models in a predictive fashion. The session will emphasize successes and limitations in current NAMs for these endpoints and highlight the priority needs for future dedicated research to improve modeling. Discussion will focus on what is needed to bring these approaches into broad regulatory use.

Introduction. Catherine Willett, Humane Society of the United States, Washington, DC.

Mechanistic Approaches to Predict Acute Mammalian Systemic Toxicity. Daniel Wilson, Dow Chemical Company, Midland, MI.

Prediction of Specific Target Organ Toxicity after Repeated Exposure (STOT-RE) Using NAMs. Mark Cronin, Liverpool John Moores University, Liverpool, United Kingdom.

Prediction of Developmental and Reproductive Toxicity Using NAMs. George Daston, Procter & Gamble Company, Cincinnati, OH.

Panel Discussion/Q&A.

The Utility of Echocardiography in Cardiac Safety Assessment

Tuesday, March 12, 3:00 PM to 4:30 PM

Chairperson(s): Jacqueline Walisser, Covance Inc., Madison, WI; and Timothy Hacker, University of Wisconsin-Madison, Madison, WI.

Primary Endorser: Cardiovascular Toxicology Specialty Section

Other Endorser(s): Drug Discovery Toxicology Specialty Section; Regulatory and Safety Evaluation Specialty Section

Echocardiography provides a noninvasive means to assess cardiac structure and function and is widely used clinically to assess left ventricular function, hypertrophy, valvular disease, and myocardial infarction. Increasingly, echocardiography has become a sought-after tool in nonclinical research to make informed decisions on intended pharmacology and/or off-target actions of test articles under development. This session will aim to provide an overview of the utility of echocardiography in nonclinical research, including the latest novel technologies, species and study design considerations, and a regulatory viewpoint on the utility of nonclinical echocardiography data in the assessment of Investigational New Drug (IND) submissions and subsequent clinical trials. The session will start with an outline of the use of small (rodents) and large (dogs, monkeys) animal echocardiography, including a description of common endpoints assessed. In addition, the first presenter will address the utility of echocardiography in healthy animals and animal models of cardiac disease as part of nonclinical safety assessment. The second presentation will address a range of anatomic, behavioral, and hemodynamic factors that
affect quantitative analyses, including common design elements used to maximize data quality and effect size detection thresholds, and potential pitfalls to avoid. The third talk will discuss how nonclinical ultrasound data generated in animals are utilized and interpreted as part of an IND submission and how these data may impact early clinical trials. The target audience is toxicologists who may have limited exposure to the utility of echocardiography in nonclinical animal studies and are looking to expand their knowledge in the area. By the end of the session, attendees should better understand the technical considerations and strategies for employing echocardiography in nonclinical animal studies and how animal-based echocardiography data generated as part of a drug safety assessment program may impact IND submission and subsequent clinical trials. Based on the fact that cardiovascular liabilities continue to be a leading cause of drug attrition in late-stage clinical trials and post-market approval, it is expected that additional measures to assess cardiac function will be of great interest to the toxicology and drug development communities.

**Introduction.** Jacqueline Walisser, Covance Inc., Madison, WI.

**Using Ultrasound to Assess Cardiac Structure and Function in Nonclinical Animal Models.** Timothy Hacker, University of Wisconsin-Madison, Madison, WI.

**Insights into Echocardiography in Drug Development.** Bari Olivier, Michigan State University, Lansing, MI.

**Echocardiography in Nonclinical Safety Assessment: A Regulatory Perspective.** Elizabeth Hausner, US FDA, Silver Spring, MD.

**Panel Discussion/Q&A.**
Tips for Improving Scientific Communication with a General Audience

Tuesday, March 12, 4:45 PM to 6:05 PM

Chairperson(s): Jonathan Shannahan, Purdue University, West Lafayette, IN; and Samantha Snow, US EPA, Durham, NC.

Primary Endorser: Postdoctoral Assembly

Other Endorser(s): Ethical, Legal, Forensics, and Societal Issues Specialty Section; Graduate Student Leadership Committee

For research to broadly and positively impact public health, it must be efficiently communicated to, and understood by, the general public. The majority of university-level scientific training focuses on performing cutting-edge research and sharing those findings with other scientists within one’s own field. In a time where information is readily accessible, ensuring effective and accurate scientific messaging through community outreach is necessary for maximizing societal impact and understanding. This is true during one-on-one conversations with nonscientists, and through interactions utilizing social and mass media. Deficiencies in the capacity to share science-related topics with nonscientists result in misinterpretation of conclusions and decreased community engagement in science. This session is designed to bring in scientific outreach experts to share tips and strategies for researchers to successfully communicate science with the general public. Speakers will focus on (1) individual interactions, (2) controlling your message, (3) the use of innovative social media platforms, and (4) effective utilization of mass media. These interactive presentations will include real-world examples of successful scientific communication as well as illustrations of common errors scientists are prone to committing. These discussions will be highly applicable to all attendees, including graduate students, postdoctoral trainees, and senior toxicologists. This session will allow both trainees and seasoned toxicologists to learn and implement this increasingly useful and necessary skill set.

Beer-Reviewed Science: How (and Why) to Talk About Your Science with People outside the Lab. Katy May, North Carolina State University, Raleigh, NC.

Science is Not Finished Until It Is Communicated. Judith Zelikoff, New York University School of Medicine, Tuxedo, NY.

Using Free Social Media Online Tools to Communicate Scientific Activities, Distribute Data, and Enhance Scientific Articles Post-Publication. Antony Williams, US EPA/NCCT, Durham, NC.

How to Communicate with and through the Media. Laura Helmuth, Washington Post, Washington, DC.
Establishing Effective Alternatives for Acute Oral and Inhalation Systemic Toxicity Testing

Wednesday, March 13, 8:00 AM to 10:45 AM

Chairperson(s): Agnes Karmaus, ILS, Research Triangle Park, NC; and Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.

Primary Endorser: In Vitro and Alternative Methods Specialty Section

Other Endorser(s): Computational Toxicology Specialty Section; Risk Assessment Specialty Section

Acute systemic toxicity testing is required by regulatory agencies worldwide, provides the basis for hazard labeling and risk management of industrial chemicals, agrochemical formulations, and pharmaceuticals, and represents the highest cumulative animal use across chemical sectors. The development of test methods that reduce or replace animal use for acute systemic toxicity tests is one of the highest priority activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which is composed of representatives from 16 US federal regulatory and research agencies that use or generate toxicological testing information. Despite the multitude of in vitro and in silico methods, a lack of regulatory acceptance of defined approaches prevents the widespread adoption of these approaches by industry. This session will demonstrate how engaging regulators and stakeholders up-front facilitates effective integration of alternatives, ensuring a path to success in reducing the use of animals in acute testing. Efforts in the United States to identify, develop, validate, and implement alternatives to the traditional acute systemic toxicity tests associated with oral and inhalation exposures will be highlighted. Overall this session will review the current status of developing alternative approaches to acute systemic toxicity testing to meet agency needs, challenges in integrating new methods, and approaches to facilitate the adoption of these alternative methods in the near term and achieve the goal of significantly reducing animal use in acute toxicity testing by 2020.

Introduction. Agnes Karmaus, ILS, Research Triangle Park, NC.


Derivation of a Dataset for Modeling Acute Oral Toxicity and Variability Assessment of In Vivo LD50 Data. Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.

International Collaboration to Build Predictive Models for Acute Oral Toxicity. Kamel Mansouri, ILS, Morrisville, NC.

In Silico and In Vitro Approaches to Assess Inhalation Toxicity Testing. Amy Clippinger, PETA International Science Consortium Ltd., Norfolk, VA.

Integrating Nonanimal Alternative Approaches to Assess the Risk to Human Health from Inhaled Materials. Jon Hotchkiss, Dow Chemical Company, Midland, MI.

Panel Discussion/Q&A.
Health authorities responsible for regulating pharmaceuticals and pesticides request studies to determine carcinogenic potential. These studies conform to Guidelines of the International Council on Harmonization (ICH S1) for drugs and OECD guidelines for pesticides. For drugs these studies are requested to be conducted when human treatment is necessary for longer than six months; for crop protection chemicals they are required for most exposure scenarios. The value of the rodent bioassays continues to be questioned because of their lack of relevance to humans. Retrospective analyses of various datasets (PhRMA, US FDA, JPMA, and EU) concluded that the outcome of these rodent studies could be predicted as follows: negative predictions can be made when carcinogenic signals such as absence of hyperplasia in a six-months study and certain pharmacological properties are absent, whereas positive predictions are possible when such signals are present. In-between compounds remain for which the outcome is equivocal and where experimental studies may add value to identify real hazards. These hypotheses stimulated ICH to evaluate compounds in a prospective way in an ongoing exercise. US EPA and the pesticide industry are similarly stimulated to consider harmonization on such alternative approaches. This symposium is intended to provide transparency into the progress being made to establish internationally harmonized approaches to enable more flexible carcinogenicity assessment strategies focused on mechanisms while reducing reliance on the two-year rodent bioassay. Case examples for pharmaceutical and pesticide development will be provided that demonstrate how successful implementation would look. The opportunities that emerging new technologies and rich scientific information sources can play to impact the future evolution of this flexible framework will be described.


Lessons Learned from Completed Submissions: Case Studies. Todd Bourcier, US FDA, Silver Spring, MD.

Leveraging New Capabilities to Optimize the Framework of Carcinogenicity Evaluation. Frank Sistare, Merck & Co., Inc., Kenilworth, NJ.

Application of Next-Generation Sequencing Approaches to Enhance Carcinogenicity Assessment of Pharmaceuticals In Vivo. Mark Fielden, Amgen, Thousand Oaks, CA.

The Chronic Cancer Bioassay Is Frequently Conducted for Pesticides When It Is Not Always Needed to Protect Human Health. Douglas Wolf, Syngenta, Research Triangle Park, NC.

Panel Discussion/Q&A.
The Role of Dynamic RNA Modifications in Environmental Response and Disease

Wednesday, March 13, 8:00 AM to 10:45 AM

Chairperson(s): Frederick Tyson, NIEHS/GEHB, Research Triangle Park, NC; and Jaclyn Goodrich, University of Michigan, Ann Arbor, MI.

Primary Endorser: Molecular and Systems Biology Specialty Section

Other Endorser(s): Mechanisms Specialty Section

This symposium will discuss how dynamic RNA modifications can interpret environmental stimuli/challenges and respond by altering gene regulation, biological pathways, and disease outcomes. Chemical modifications of proteins, DNA, and RNA nucleoside moieties appear to have critical roles in regulating gene expression. These chemical modifications are central to the field of functional RNA modifications and emerging evidence suggests these modifications have critical roles in basic biological processes. These include: embryonic stem cell differentiation, excitotoxic cell death, development, intergenerational inheritance of acquired traits, regulation of RNA stability, temperature adaptation, meiotic progression, and regulation of RNA-RNA and RNA-protein binding interactions. A small number of covalent RNA modifications have been studied extensively, and recent evidence suggests that other newly discovered RNA modifications have interesting biological and disease functions in mammals. Moreover, recent studies have identified N6-methyladenosine (m6A) sites in thousands of human mRNAs, suggesting that this modification may play a role in regulation of alternative splicing and gene expression. The impact of the environment on chemical modifications of RNA molecules (the epitranscriptome) in the development of adverse human health outcomes is relatively unexplored. Technology advances in recent years have accelerated the detection of RNA modifications, and the RNA Modification Database currently lists approximately 100 RNA modifications identified in eukaryotic cells. This database also reveals transfer and ribosomal RNA are heavily modified, and many of these same modifications occur in messenger RNA and non-coding RNAs (including long non-coding and microRNAs). The function of most of the modifications found in messenger and non-coding RNAs remains a mystery, despite their potential to influence RNA properties and functions, including RNA stability, trafficking, localization, activity (enzymatic, sensing, or regulatory), and interactions with other molecules. This session will bring together toxicologists with investigators in the emerging area of functional RNA modifications to discuss the state-of-the-science as well as to identify research opportunities to interrogate how environmental exposures impact this layer of cellular regulation. Questions this session will address include: Have technologies for assessing RNA modifications matured enough to apply them to investigate how environment agents and exposures impact the role of functional RNA modifications and contribute to adverse health outcomes? Does the latest research suggest diverse environmental exposures can modify functional RNA modifications and/or the readers, writers, and erasers of these modifications? Was evidence presented that suggested or confirmed that stressors can have impacts on phenotypes through RNA modification mediated mechanisms? How can toxicologists leverage knowledge about epitranscriptomics to develop new biomarkers for toxicity or targets for therapeutic intervention?

**Introduction.** Frederick Tyson, NIEHS/GEHB, Research Triangle Park, NC.

**RNA Methylation in Gene Expression Regulation.** Chuan He, University of Chicago, Chicago, IL.

**Structure and Function of RNA Methyltransferases.** Yunsun Nam, University of Texas Southwestern Medical Center, Dallas, TX.

**Epigenetic Inheritance of Acquired Traits through Sperm RNAs and Associated RNA Modifications.** Qi Chen, University of Nevada Reno School of Medicine, Reno, NV.

**Diverse Environmental Stresses Relocalize m6A RNAs and m6A-Binding Proteins to Stress Granules to Control Stress-Induced Translation Pathways.** Samie Jaffrey, Weill-Cornell Medical College, Cornell University, New York, NY.

**Epitranscriptomic Marks Translationally Regulate Stress Response Programs to Protect against Environmental Insults.** Thomas Begley, University at Albany, State University of New York, Albany, NY.
A Sharp Stick in the Eye: Understanding and Managing Ocular Findings in General Toxicology Studies

Wednesday, March 13, 8:00 AM to 10:45 AM

Chairperson(s): Evan Thackaberry, Ra Pharmaceuticals, Cambridge, MA; and Vladimir Bantseev, Genentech, Inc., South San Francisco, CA.

Primary Endorser: Ocular Toxicology Specialty Section

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section

Unexpected ocular findings in general toxicology studies represent a unique challenge in pharmaceutical drug development. Eye lesions are uniquely monitorable in this setting, often using the same techniques that are applied in clinical studies. This allows for detailed assessment of the dose-response and onset of lesions as well as their functional impact. However, understanding the specialized grading scales and imaging modalities is key to interpreting these data. Additionally, many tissues of the eye, particularly the retina, are terminally differentiated and unable to regenerate following toxic insult. This makes the detection, characterization, and mechanistic understanding of ocular lesions caused by novel therapeutics of vital importance for an assessment of human risk prior to clinical trials. The objective of this session will be to focus on adverse ocular findings on general toxicology studies for non-ophthalmology products. The first presentation will focus on the common ocular assessments used on these studies and frequently observed ocular lesions. This will be followed by three case studies in which unexpected ocular findings were observed on general toxicology studies, with a focus on the sponsor’s investigative and regulatory strategy to address these findings. Finally, a speaker from the US FDA will provide a perspective on regulatory expectations for therapies with adverse ocular effects.

Introduction. Evan Thackaberry, Ra Pharmaceuticals, Cambridge, MA.

Evaluating the Endangered Eye: Ocular Assessment in Preclinical General Toxicity Investigations. Seth Eaton, Ocular Services On Demand (OSOD), Madison, WI.

Ocular Toxicity with Microtubule Inhibitor Containing Antibody Drug Conjugates: Nonclinical to Clinical Translatability Case Examples. Nicola Stagg, Genentech, Inc., South San Francisco, CA.

Lessons Learned in How to Manage Ocular Findings: A Case Study. Brenda Smith, Allergan, Irvine, CA.

Unexpected Ocular Pathology Findings in Systemically Administered Drugs: Two Case Studies. Ken Schafer, Vet Path Services, Indianapolis, IN.

Transient Retinal Changes following Systemic Small Molecule Administration: Case Study from Subchronic and Chronic Toxicology Studies. Christopher Frantz, Genentech, Inc., South San Francisco, CA.

Panel Discussion/Q&A.
Seizure liability remains a significant cause of attrition in drug discovery and development, leading to loss of competitiveness, delays, and increased costs. Current detection methods usually rely on observations made in the nonclinical rodent and nonrodent studies required to support clinical trials. These could be central nervous system (CNS)-related signs such as tremors or other abnormal movements, but these signs can be misdiagnosed or misinterpreted by inexperienced operators. Thus, confirmation of drug-induced seizure or seizure-like activity requires a follow-up electroencephalogram (EEG) study. Some progress has been made in in-life detection of seizure using automated video systems that record and analyze animal movements, looking for abnormalities. Nonetheless, it would be far preferable to have an earlier prediction of seizurogenic risk that could be used to eliminate liabilities early in discovery while there are still options in chemistry. Two approaches offer exciting opportunities. Microelectrode array is now able to detect seizurogenic signals in iPSC-derived cortical neural stem cells differentiated to electrically active cortical neurons. This offers great potential to screen for seizurogenic liability in an in vitro system. A second approach could be based on an understanding of the neuronal ion channels implicated in the seizurogenic response. There is clear evidence for the involvement of ion channels in seizure. Genetic studies have pointed to a role for voltage-gated sodium and potassium channels and the ligand-gated ion channels, GABAA and nicotinic acetylcholine receptors. Pharmacologically, a number of ion channel modulators are known to be seizurogenic, such as Chlorpromazine. Recently, great progress has been made in developing these in vitro seizure models and in characterizing the ion channels both at the expressionional and at the functional level. These data may provide the opportunity to panelize seizure by creating a panel of ion channel assays that predict seizure, linked to an in vitro assessment, with the ultimate aim of eliminating compounds predicted to be associated with the pro-seizurogenic state. The regulatory community has great expertise and experience of how to shape such work for decision-making from lessons learned from implementation of similar approaches in derisking cardiovascular liability. This session will address the issue, the basic science, and the regulatory context. It is relevant to academia, industry, CROs, and regulators who wish to learn more about these exciting, new, and high-impact developments in drug discovery and development.

- **Seizure Liability in Drug Discovery and Development: Current State of Play.** Jean-Pierre Valentin, UCB, Braine-l’Alleud, Belgium.
- **Identification and Confirmation of Seizure Liability In Vivo: The Importance of Behavioral Monitoring and EEG Recording.** Alison Easter, Biogen, Cambridge, MA.
- **Development of Seizure Prediction Methods Using MEA System in Human iPS Cell-Derived Neurons.** Ikuro Suzuki, Tohoku Institute of Technology, Tohoku, Japan.
- **Using Ion Channels to Panelize Seizure: Where Are We Up To?** Michael Morton, ApconiX, Alderley Edge, United Kingdom.
- **Panel Discussion/Q&A.**
All nerve agents act by inhibiting the enzyme acetylcholinesterase (AChE), which is responsible for catalyzing the breakdown of acetylcholine (ACh) at neuromuscular junctions and at synapses in the central and peripheral nervous systems. In addition, the process of "aging" results in a monoalkylphosphonyl product which does not reactivate spontaneously and cannot be reactivated by pyridinium oximes, such as pralidoxime and obidoxime. Nerve agents were employed most recently in an attack on Khan Sheikhoun, Syria, in April 2017. VX was used as a weapon of assassination on February 13, 2017, when Kim Jong-nam, was killed at Kuala Lumpur International Airport. In Salisbury, England, on March 4, 2018, Sergei Skripal, his daughter Yulia, and a policeman investigating the incident were severely poisoned following exposure to a Novichok agent. Subsequently, on June 30, 2018, two more individuals were severely poisoned with the same Novichok agent, one of whom died. All these releases indicate that countries and their clinicians must be prepared adequately to treat casualties optimally from nerve agent exposure. This requires an understanding of the mechanisms of toxicity of these agents, the factors that influence their clinical impact, and knowledge of potential treatments. Although the signs and symptoms manifested by exposed individuals will aid diagnosis, reliable point-of-care diagnostic systems will expedite triage and the application of appropriate medical countermeasures. Most of these systems are based on measurement of acetyl- or butyrylcholinesterase activity, but more recently an easy-to-use lateral flow assay has been developed that can be used for both rapid point-of-care diagnosis, as well as for detection of submicrogram amounts of nerve agents in/on various matrices. However, unequivocal verification of an exposure requires a variety of specialized techniques, and the utility of these methods will be exemplified by the analysis of various samples from the Syrian Arab Republic conflict in April 2013. Much research is underway to improve the current treatment regimens, which include an anticholinergic drug (e.g., atropine) to antagonize the effects of excess ACh at muscarinic effector sites, the use of an oxime (e.g., pralidoxime, obidoxime, and HI-6) to reactivate nerve agent-inhibited AChE, and a benzodiazepine to prevent or stop nerve agent-induced seizures. Four innovative treatment approaches will be described during the session. First, the development of catalytic scavengers: multiple candidate enzymes on different structural scaffolds have been produced in an effort to develop a single enzyme capable of catalyzing the hydrolysis of a broad spectrum of organophosphorus (OP) compounds into nontoxic products. The most promising candidate enzyme platform is the bacterially produced recombinant variant of organophosphorus hydrolase from B. diminuta. In in vivo studies, two different organophosphorus hydrolase variants were capable of providing protection against at least 2 x LD50s of all of the OPs tested. Second, a series of novel substituted phenoxalkyl pyridinium oximes have been produced, which reduce brain AChE inhibition in rats treated with high-dose challenges of OP compounds. These novel oximes also have shortened the time to cessation of OP-induced seizure-like behavior on the day of OP challenge and have reduced neurodegeneration observed four days after the challenge by such neural markers as NeuN. These oximes when delivered intramuscularly show a high ability to provide 24-hour survival from lethal OP dosages and they have a half-life of 2.5 hours or greater in the blood stream of the rat, and therefore have promising pharmacokinetics. Third, the use of the bispyridinium non-oxime compound MB327 increased the survival of rats poisoned with soman, without reactivation of AChE. Moreover, it has been shown inhuman and rodent muscle tissue that paralysis of the respiratory muscles could be restored partially by MB327. In addition, MB327 and several structurally analogous compounds were able to restore function of nicotinic receptors (Torpedo californica muscle-type and human a7 subtype) after desensitization (demonstrated with electrophysiological techniques using patch clamp and SSM-based electrophysiology). Moreover, molecular modeling allowed identification of a new allosteric binding site close to the transmembrane domain of the nicotinic receptor. From these data, it may be concluded that by using MB327 and its analogues as a template, new structures with improved binding properties may be able to antagonize paralysis of blocked muscle function, without reactivation of inhibited AChE. Fourth, improvement of nerve agent elimination by small molecule scavengers might further contribute a beneficial effect. Indeed, modified cyclodextrins are able to bind the highly toxic (-) isomere of GF and calixarenes are able to enhance degradation of VX by a factor of 3500.

Allister Vale, University of Birmingham, Birmingham, United Kingdom.
(continued on next page)
Diagnosis and Verification of Nerve Agent Poisoning. Daan Noort, Netherlands Organization for Applied Scientific Research (TNO), Rijswijk, Netherlands.


Blood-Brain Barrier Penetrating Reactivators of Organophosphate-Inhibited Acetylcholinesterase (AChE). Janice Chambers, Mississippi State University, Mississippi State, MS.

Alternative Approaches for Therapy of Nerve Agents. Horst Thiermann, Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany.

Panel Discussion/Q&A.

Pregnant and Vaping: Knowns and Unknowns of Reproductive and Developmental Toxicity Related to Electronic Cigarettes

Wednesday, March 13, 8:00 AM to 10:45 AM

Chairperson(s): Alexandra Noël, Louisiana State University, Baton Rouge, LA; and Ilona Jaspers, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Primary Endorser: Reproductive and Developmental Toxicology Specialty Section

Other Endorser(s): Ethical, Legal, Forensics, and Societal Issues Specialty Section; Inhalation and Respiratory Specialty Section

Electronic cigarettes (e-cigs) are vehicles for inhaled delivery of nicotine and are considered by some to be smoking cessation aid devices, although they are not approved by US FDA for cessation treatment, nor even considered as nicotine replacement therapy (NRT). The benefits of e-cigs as nicotine replacement vehicles are countered by an expanding body of knowledge regarding potential health hazards and social consequences. E-cig aerosols have a unique physical and chemical composition that is different from that of cigarette smoke, although both aerosols contain nicotine and other similar toxicants. At present, there are very limited regulatory or legal processes overseeing the production and sales of e-cig devices. Thus, the general safety of e-cigs regarding human health is still a matter of controversy. According to the CDC, e-cig use among high school students increased by more than 300% between 2013 and 2014, and its use has continued to increase. The 2016 Surgeon General’s report labeled e-cig use among adolescents and young adults a major public and societal health concern. The public perception of e-cigs as a healthier alternative to conventional cigarettes has led to the recent increase in e-cig use among youth and young adults, including women of childbearing age. Although research is emerging around e-cigs in general, there continues to be a lack of scientific evidence regarding the safety and risks of e-cig use on maternal and fetal health; however, adverse health effects of nicotine on maternal and fetal outcomes are well documented. In the US, more than 10% of women smoke during pregnancy, and recent national surveys show that this proportion is similar for the use of e-cig devices. Controversy, however, over e-cig use during pregnancy is being hotly debated between US and UK regulators. Currently, there are no guidelines for use of e-cigs during pregnancy. This highlights the urgent need to bridge the clinical and scientific knowledge gap related to e-cig use during pregnancy. Whether e-cig use during pregnancy is safer and represents a better risk-to-benefit ratio for the developing fetus than conventional cigarettes is unclear due to lack of studies. This session provides a unique focus on the knowns and unknowns of e-cig use during pregnancy, including ethical and societal implications. A panel discussion incorporating both US and UK basic research and policy frameworks will represent a strong base for discussing whether e-cig use could be a reasonable alternative for pregnant smokers who are otherwise unable to quit.

Introduction. Alexandra Noël, Louisiana State University, Baton Rouge, LA.


Lessons Learned about Prenatal E-cigarette Exposure from In Utero Exposures in Animal Models. Judith Zelikoff, New York University School of Medicine, Tuxedo Park, NY.
Maternal Exposure to Combustion-Derived Aerosols Is Associated with Obesity in Offspring: Implications for In Utero Exposures to E-cigarettes. Stephania Cormier, Louisiana State University, Baton Rouge, LA.


Summary. Alexandra Noël, Louisiana State University, Baton Rouge, LA.

Understanding the Impact on the Immune System of Occupationally Relevant Exposures to Multiwalled Carbon Nanotubes

Wednesday, March 13, 8:00 AM to 10:45 AM

Chairperson(s): Nigel Walker, NIEHS/NTP, Research Triangle Park, NC; and Victor Johnson, Burleson Research Technologies, Inc., Morrisville, NC.

Primary Endorser: Immunotoxicology Specialty Section

Other Endorser(s): Inhalation and Respiratory Specialty Section; Nanotoxicology Specialty Section

Extensive efforts in research and development have led to extraordinary advances in nanoscience, nanotechnology, and the utility of nanomaterials. Uses of nanomaterials range from structural improvements, to building materials, to improvement in medical devices and drug delivery. As a result, there has been an increase in the potential for human exposure to nanomaterials not only inadvertently in occupational settings, but also in consumers and patients that utilize nanomaterials. Multiwalled carbon nanotubes (MWCNT) are a class of nanomaterials used for a variety of applications including structural enhancement of building materials and sports equipment, and for improvement of electrical and thermal conductivity for electronics. Animal studies have largely focused on the health effects following pulmonary exposure in rodent models. Many of these studies have demonstrated the occurrence of pulmonary inflammation associated with fibrotic changes in the airways. However, the majority of these studies investigated pulmonary exposure at dose levels that are significantly higher than occupational exposure levels. Recent studies have also demonstrated that pulmonary exposure to carbon nanotubes can result in systemic effects (cardiovascular changes and immunotoxicity), including increased expression of inflammatory cytokines genes in splenic lymphocytes in rats. These findings suggest that carbon nanotubes could target the immune system and raise the concern that low-level exposure may impact host resistance to infections or development of neoplastic diseases or increase susceptibility to allergy or autoimmune diseases. To address this issue, a consortium of academic and federal scientists initiated an integrated approach to investigate the toxicity of low-level occupationally relevant exposures to a representative high-purity “long and thin” aggregated MWCNT. Characterization of this MWCNT shows that it aggregates into micron-sized “cotton ball” structures that morphologically appear similar to MWCNTs sampled in the workplace. Key features of the approach were the well-characterized, GLP-compliant inhalation exposure system used for treatment of the rats and the partnership between the federal and academic laboratories assessing different models of impacts of the exposure on the immune system. Importantly, all of the immunotoxicity studies that will be discussed in this session were obtained from the same exposure cohorts, thereby enhancing the ability to integrate results across all studies and participating laboratories. The session will identify the occupational exposures to MWCNT, put the experimental work into a human-relevant context, and then highlight the complementary approaches undertaken by the different groups to characterize the effects of MWCNT on innate and adaptive immune responses following low-dose pulmonary inhalation exposures.

Introduction. Nigel Walker, NIEHS/NTP, Research Triangle Park, NC.

Perspectives from the Field: Occupational Exposures to Carbon Nanotubes in the US. Matthew Dahm, NIOSH, Cincinnati, OH.

Pulmonary and Systemic Immunotoxicity following Inhalation of Multiwalled Carbon Nanotubes. Victor Johnson, Burleson Research Technologies, Inc., Morrisville, NC.

Consequences of Inhalation Pre-exposure to Multiwalled Carbon Nanotubes on Airway Inflammation and Fibrosis Induced by House Dust Mite Allergen. James Bonner, North Carolina State University, Raleigh, NC.

Characterization of Inflammatory Responses and Redistribution of MWCNT following Aerosol Exposure in B6C3F1/N Mice. Andrij Holian, University of Montana, Missoula, MT.

The face of regulatory toxicology is undergoing a makeover in the 21st century with the encouragement of new approach methodologies. However, is the way the scientific community accesses and understands uncertainty adapting to developing methodologies? Historically, toxicology testing for the assessment of human health has used animals, in which uncertainty factors were incorporated to address issues such as interspecies differences and species-specific mechanism of action. These uncertainties are in addition to the standard scientific uncertainties that exist with any experimental data. With the international push to accept alternative nonanimal testing in lieu of traditional in vivo testing, now is the time to understand acceptable uncertainty for developing methods. However, if uncertainty cannot be assessed and addressed in the same manner as the scientific community is comfortable with for in vivo data, what levels and expressions of uncertainty would be acceptable to make a regulatory decision with a new approach methodology for a specific regulatory context? This roundtable will discuss how uncertainty has historically been quantified, how it differs between methods (in vivo/in vitro/in silico), and how it has been addressed and should be addressed in order to facilitate development and implementation of new approach methodologies. We dare to broach the cultural barriers to accepting new approach methodologies in safety and risk assessment. We also intend to incite dialogue to address what types and subsequent levels of uncertainty are likely or tolerable in 21st-century toxicology.

**All Models Are Wrong, but Some Are Useful**! Kim Boekelheide, Brown University, Providence, RI.

**Ideal Ingredients in a Quantified Application of Uncertainty.** Greg Paoli, Risk Sciences International, Ottawa, ON, Canada.

**Industry Perspective: A Fit-for-Purpose Scientific Confidence Framework Applicable to New Assessment Methods.** Richard Becker, American Chemistry Council, Washington, DC.

**Characterization and Integration of Uncertainty across Alternative Methods for Hazard, Toxicokinetics, and Exposure.** Russell Thomas, US EPA/ORD, Durham, NC.

**Assessment and Communication of Uncertainty: Confidence in and Acceptance of Models and New Approach Methodologies.** Andrea Richarz, European Commission Joint Research Centre, Ispra, Italy.

**Defining the Domain of Applicability for In Vitro-Based Predictions.** Rebecca Clewell, ToxStrategies, Inc., Durham, NC.

**Panel Discussion/Q&A.**
Reliable information about formal toxicology curricula and education-training in Africa is very scarce. Illustrative of that example is the fact that in the last 20 years there has been few publications (fewer than five) that have discussed toxicology education in South Africa and veterinary toxicology education in Africa. The continent of Africa is in a stage of rebirth after a long time in stagnation. Africa is now home to seven of the world’s 10 fastest growing economies. Africa is very rich in human capital, and today nearly 50% of Africans are under age 15. Africa has the fastest-growth rate in the world (due to dropping child mortality and high fertility), with the continent expected to have an estimated 2.8 billion people by 2060. Overall, the education in Africa is slowly improving. However, there is outstanding improvement in children’s primary education. The number of children enrolled in primary schools more than doubled, from 62 million to 149 million children, within 22 years (1990–2012). A systematic review indicates that university education continues to pose a significant challenge in Africa. In the continent’s 10 most-populous nations, there are 740 universities serving some 660 million Africans. This ratio in terms of the number of universities compared to the US represents a meek 10%, with the US has some 5,300 universities and colleges serving a population of over 323 million people. Historically Africa hosts the two oldest universities in the world: the University of Al Qarawiyyin in Fez, Morocco, which opened in AD 859, and Al-Azhar University in Egypt, part of the larger complex of institutions associated with Al-Azhar Mosque and which currently enrolls two million students. This session will provide an overview of the educational and training challenges within the toxicology diaspora and present research findings from studies that can inform the approach that SOT Special Interest Groups (SIGs) take to address the dilemma going forward. Desired outcome: as the majority of presenters in this session have experience in improving the toxicology and risk assessment training in various parts of Africa, the presenters will share this experience and explore innovative strategies to address the educational and training curricula in Africa despite the lack of meaningful investment in educational and research infrastructure by most African governments. A summary of the session presentations and recommendations will be shared with various organizations working in Africa.


Roles of Nonprofit Organizations in Promoting Toxicology and Risk Assessment Training in Africa. Bernard Gadagbui, TERA, Cincinnati, OH.

The Relevance of Veterinary Toxicology in Africa. Wilson Rumbeiha, Iowa State University, Ames, IA.

African Needs for Training and Research in Environmental Toxicology and Occupational Health. Olorunfemi Adetona, Ohio State University, Columbus, OH.

Web-Based Global Classes, New Model for Toxicology and Risk Assessment Education: Advantages and Challenges. Osama S. El-Tawil, Cairo University, Giza, Egypt.

Panel Discussion/Q&A.
Stepping Out of the Lab: Maximizing Access and Experience for Internships in Toxicology

Wednesday, March 13, 11:00 AM to 12:20 PM

**Chairperson(s):** Natalie Johnson, Texas A&M University, College Station, TX; and Amy Roe, Procter & Gamble Company, Cincinnati, OH.

**Primary Endorser: Education Committee**

**Other Endorser(s):** Career Resource and Development Committee; Graduate Student Leadership Committee

A major goal of the SOT Education Committee is to expand opportunities for students to engage in internships within industry, government, and nonprofit organizations. Immersion in internships provides students unique appreciation of the day-to-day activities of toxicologists and paths for success in these sectors. Such opportunities can help students establish their professional network, build confidence in career choices, and ultimately better prepare for transitioning into these sectors upon graduation. While numerous industries and governmental agencies have internship programs, or comparable opportunities, identifying these opportunities can be challenging. There are also barriers associated with funding, mentor buy-in, timing of the internship relative to the student’s graduate training, and feasibility for international student participation. The goal of this session is to bring together the various stakeholders—graduate students, faculty, and those hosting interns—to discuss best practices for developing internships, and strategies for increasing the number of available internships as well as improving awareness and access to available internships. The session will consist of five presentations followed by a group discussion on strategies that the SOT Graduate Education Subcommittee might develop to increase internship opportunities and overcome barriers for industry and government to host interns, and for graduate students to attain highly competitive internships. The formal talks will begin with a presentation by an individual who completed an internship as a graduate student discussing the benefits and logistical challenges of internship experiences, followed by presentations from representatives of two graduate training programs that have used different approaches for identifying internship opportunities for their graduate trainees, and representatives from industry and government discussing the opportunities and challenges of developing and advertising internships. Throughout this session, audience participation and feedback will be enabled with real-time polling and discussion.

**Benefits and Challenges of Performing an Internship as a Graduate Student.** Agnes Karmaus, ILS, Research Triangle Park, NC.

**“Real-World” Training Experience through Internships at the Interface of Toxicology and Regulatory Science.** Natalie Johnson, Texas A&M University, College Station, TX.

**Private-Public Partnerships as a Foundation for the Training of Toxicology Students.** Lauren Aleksunes, Rutgers, The State University of New Jersey, Piscataway, NJ.

**Industry Perspective on Providing Successful Training Opportunities to Graduate Students.** Amy Roe, Procter & Gamble Company, Cincinnati, OH.

**Exploring Opportunities Provided through Government Agency Internships.** Shelley DuTeaux, California Department of Pesticide Regulation, Sacramento, CA.

**Moderated Group Discussion.** Aaron B. Bowman, Purdue University, West Lafayette, IN.
Consideration for Safety Assessment of Chemically Synthesized Therapeutic Peptides: A Drug Development Paradigm between the Large and Small

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Mayur Mitra, Genentech, Inc., South San Francisco, CA; and Evan Thackaberry, Ra Pharmaceuticals, Cambridge, MA.

Primary Endorser: Biotechnology Specialty Section

Other Endorser(s): Drug Discovery Toxicology Specialty Section; Regulatory and Safety Evaluation Specialty Section

Thousands of naturally occurring peptides act as key signaling molecules and thereby regulate crucial physiological pathways. Due to their high target selectivity and attractive intrinsic properties, novel chemically synthesized peptides continue to gain interest as an effective modality against undruggable targets. Currently, over 60 therapeutic peptides have gained worldwide approval and approximately 150 candidates are in clinical development. As with any other novel technology, development and safety assessment of chemically synthesized peptides present with an array of complex challenges. Additionally, there is a lack of specific regulatory guidance for peptide development. The industry relies on associating existing small molecule [ICH M3(R2)] and biologic [ICH S6(R1)] guidances to develop therapeutic peptides. This symposium has been designed to provide a general scientific and strategic framework for safety assessment of therapeutic peptides. The session will begin with an introduction to peptides and give insights to their history, current status, and future while reviewing the advantages and disadvantages of this modality. This will be followed by discussions of scientific and regulatory considerations for general toxicology, genetic toxicology, and impurity assessment. Specifically, the discussions will focus on navigating the unique challenges associated with peptide development, such as short plasma half-life and rapid clearance, presence of non-natural amino acids, and immunogenicity assessment, among others. Finally, the symposium will conclude with a case study of chronic toxicology assessment of a peptide-based drug, Dasiglucagon, a glucagon analogue, which is currently in late-stage development. Toxicologists working in academia, federal, and pharmaceutical industries and researchers interested in peptide drug development will benefit from this scientific symposium.

The Past, Present, and Future of Peptide Therapeutics. Evan Thackaberry, Ra Pharmaceuticals, Cambridge, MA.


Impurity Limits for Synthetic Peptides: A Nonclinical Approach. Stephanie Leuenroth-Quinn, US FDA, Silver Spring, MD.

Genotoxicity Testing of Peptides. Laura Custer, Bristol-Myers Squibb, New Brunswick, NJ.

Dasiglucagon, a Glucagon Analogue: Toxicity Profile following Chronic Administration in Rats and Dogs. Mikael Elander, Zealand Pharma, Copenhagen, Denmark.

Panel Discussion/Q&A.
Role of Oxidative Stress in Health and Disease: Mechanisms, Methods of Detection, and Biomarkers

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Bhagavatula Moorthy, Baylor College of Medicine, Houston, TX; and Lynette Rogers, Research Institute at Nationwide Children's Hospital, Columbus, OH.

Primary Endorser: Molecular and Systems Biology Specialty Section

Other Endorser(s): Mechanisms Specialty Section

Oxidative stress is an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling, which in turn leads to cellular injury. Damage mediated by reactive oxygen species (ROS) can have a profound effect on many cellular functions. Oxidative stress occurs with many toxic exposures and appears to provide a mechanistic link between exposure and disease, yet free radical scavenging antioxidants showed little health benefit in large-scale human interventional trials. The major goal of this symposium is to discuss the molecular and cellular mechanisms by which ROS, including free radicals, contribute to oxidative stress and alter various signaling pathways, which could in turn lead to toxicities in target organs, and ultimately human diseases including pulmonary diseases such as bronchopulmonary dysplasia (BPD), acute respiratory distress syndrome (ARDS), and cancer. The novel aspect of the proposed symposium is to discuss the chemistry of ROS, the ultrasensitive methods to detect and analyze them in vivo, and the mechanisms by which they contribute to organ toxicities. The research presented here will offer opportunities for preventative and therapeutic interventions in human diseases that are caused by oxidative stress. The recent findings of the novel roles of ROS in multiple human diseases warrant the need for a symposium to discuss the latest mechanistic research in this area and its impact on human health. Specifically, the symposium will discuss methods of detection and measurement of oxidative stress including integrated metabolomics, the role of epigenetic mechanisms in the developing lung, the mechanistic role of cytochrome P450 (CYP) enzymes and Nrf2 in oxidative stress, and novel biomarkers to distinguish between oxidative stress and inflammation. The symposium will also discuss new opportunities for translational research, which leads to the development of rational strategies (e.g., discovery of novel drugs in collaboration with pharmaceutical industry) for the prevention and/or treatment of human diseases by oxidative stress. Thus, this symposium would be of great interest to toxicologists who are focusing on the mechanisms of toxicity of a wide variety of chemicals that mediate toxicity by mechanisms entailing oxidative stress.

Introduction. Bhagavatula Moorthy, Baylor College of Medicine, Houston, TX.

ROS-Mediated Epigenetic Changes in Developing Lungs. Lynette Rogers, Research Institute at Nationwide Children's Hospital, Columbus, OH.

NRF2, Oxidative Stress, and Inflammatory Lung Injury. Donna Zhang, University of Arizona, Tucson, AZ.

Validation of Best Detection Methods for Oxidized Macromolecules In Vivo and in Smokers. Maria Kadiiska, NIEHS, Research Triangle Park, NC.

Redox Metabolism and Oxidative Stress. Dean Jones, Emory University, Atlanta, GA.

Mechanistic Role of Cytochrome P4501A and 1B1 Enzymes in the Metabolism of Reactive Oxygen Species (ROS)-Mediated Formation of Lipid Hydroperoxides: Implications for Hyperoxic Lung Injury and Human ARDS. Bhagavatula Moorthy, Baylor College of Medicine, Houston, TX.

Panel Discussion/Q&A.
Understanding the Utility of In Vitro Developmental Toxicity Assays and Building Integrated Testing Strategies

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Jessica Palmer, Stemina Biomarker Discovery, Inc., Madison, WI; and Thomas Knudsen, US EPA/ORD, Research Triangle Park, NC.

Primary Endorser: In Vitro and Alternative Methods Specialty Section

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section; Reproductive and Developmental Toxicology Specialty Section

The performance of many alternative methods for developmental toxicity testing has been evaluated over the last 20 years; however, their application as new approach methods (NAMs) in a regulatory setting is still poorly defined. Several groups and regulatory agencies are working on ways to address this limitation through the development of strategic roadmaps and updating current testing requirements, including ICCVAM, US FDA, US EPA, ICH, ECVAM, JACVAM, and the EU-ToxRisk consortium. Given the numerous complex processes involved in fetal development, it is unlikely that a single assay or adverse outcome pathway (AOP) concept will be sufficient for understanding and/or predicting the developmental toxicity potential of chemicals. Defining the applicability domain of each NAM, in terms of both chemical and biological space, establishing scientific confidence in their validity, and characterizing how they are best used in integrated testing strategies will be key for gaining regulatory acceptance of alternative methods. Evaluating well-defined groups of reference chemicals, such as the list proposed in the draft ICH Guideline S5(R3) on Detection of Toxicity to Reproduction for Human Pharmaceuticals or environmental chemicals identified by ICCVAM with robust animal data in multiple species, can help provide insight into the limitations of NAMs and how they can be combined. Systematic review techniques can integrate large sets of information from the scientific literature to identify high-quality studies and develop a weight of evidence approach for the application of NAMs. This session will highlight how the use of reference chemicals, systematic review, and evolving validation practices can be used to define the utility of NAMs, to develop integrated testing strategies, and will inform the discussion on how these approaches can help the field move toward regulatory acceptance. Experts from industry, academia, and government will present the results from a broad spectrum of reference chemicals (pharmaceutical, agrochemical, industrial, etc.) evaluated with different NAMs to demonstrate how these can be used to define the applicability domain of an assay.


Retrospective Analysis: Can Existing Literature Be Used to Compare the Results from the Zebrafish to Mammalian Embryotoxicity Tests? Katya Tsaioun, Johns Hopkins University Center for Alternatives to Animal Testing (CAAT), Baltimore, MD.


EU-ToxRisk DART Case Study Evaluating a Chemical Series across Multiple NAMs. Dinant Kroese, Netherlands Organization for Applied Scientific Research (TNO), The Hague, Netherlands.

Current and Future Opportunities for US Regulatory Application of Developmental Toxicity NAMs. Nicole Kleinstreuer, NIEHS/NICEATM, Research Triangle Park, NC.

Panel Discussion/Q&A.
Workshop Sessions | Wednesday

Air Pollution-Induced Cardiovascular Toxicity: Endothelial Progenitor Cells as Critical Mediators

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Petra Haberzettl, University of Louisville, Louisville, KY; and Christian Heiss, University of Surrey, Guildford, United Kingdom.

Primary Endorser: Stem Cells Specialty Section

Other Endorser(s): Cardiovascular Toxicology Specialty Section; Inhalation and Respiratory Specialty Section

Exposure to ambient air pollution is a leading cause of death worldwide. It has been linked globally to 7 million premature deaths and $5 trillion in costs per year. With continuing industrialization and urbanization, this disease burden is expected to increase even further. Interestingly, the majority of air pollution-associated deaths are due to cardiovascular disease (CVD). It has been estimated that in 2016, exposure to ambient and household air pollution combined was responsible for 3.5 million cardiovascular deaths. Because of this, air pollution exposure is now recognized as a modifiable risk factor that contributes to cardiovascular morbidity and mortality. Regardless of the strong evidence that air pollution exposure increases the risk for developing CVD, it remains unclear how the exposure to polluted air induces cardiovascular injury. Previous work has shown that chronic exposure to polluted air is associated with decreased endothelial function, suggesting that long-term inhalation of air pollution might result in endothelial injury and dysregulation of vascular homeostasis—effects that could accelerate CVD or trigger adverse cardiovascular events. Current research suggests that vascular homeostasis and endothelium health are maintained, at least in part, by endothelial progenitor cells (EPCs). These cells are a subpopulation of pro-angiogenic cells that reside in the bone marrow and circulate in the peripheral blood. Upon hypoxia or vascular injury, EPCs are mobilized from the bone marrow and home to the site of tissue damage where they contribute to vasculogenesis and/or angiogenesis either through terminal differentiation into mature endothelial cells or by paracrine stimulation of wound healing processes. Interestingly, recent studies show that EPCs are early and direct targets of air pollutant exposure. For instance, air pollution-induced impairments in EPC number and function have been found in humans exposed to particulate or volatile air pollution and in controlled exposure studies in rodents. These exposure studies demonstrated that inhalation of polluted air affects both circulating and bone marrow EPCs. This is important because chronically low circulating EPC levels and EPC dysfunction have been associated with vascular dysfunction and an increase in the risk and severity of CVD. Moreover, treatments that improve the number and function of EPCs (e.g., exercise, antihypertensive drugs) attenuate cardiovascular dysfunction. Because of the critical and non-redundant roles of EPCs in vascular health, air pollution exposure-induced EPC depletion and dysfunction could disturb vascular maintenance and repair, impairing vascular function, and consequently increase the risk for CVD. Hence, addressing how air pollution exposure induces EPC depletion and dysfunction is of high significance because it would help to discern the specific mechanism by which exposure to polluted air increases the risk for CVD. Understanding such mechanisms is important to develop effective therapeutic interventions and evidence-based regulations to mitigate against the major harmful health effects of air pollution. This session will highlight human studies and animal research that investigate the effects of air pollution exposure on EPCs. The specific presentations of the session will show that (1) inhalation of secondhand smoke modulates EPC number and function in healthy nonsmokers; (2) acute exposure to increased levels of ambient fine particulate matter (PM2.5) or the exposure to volatile organic components (benzene, acrolein) of polluted air are associated with changes in the number of these circulating pro-angiogenic cells; (3) the exposure to metal-rich particles impairs circulating EPC levels in humans and decreases number and function of bone marrow derived EPCs in mice; and (4) exposure to concentrated PM2.5 (CAP), by inducing oxidative stress, impairs circulating EPC levels and induces an anti-angiogenic dysfunctional EPC phenotype with a reduced ability to promote vascular tissue repair. Taken together, this session will provide a comprehensive overview that summarizes novel aspects and new mechanistic insights to understand the adverse effects of air pollutant exposure on cardiovascular health associated with changes in EPC number and function.

Introduction. Petra Haberzettl, University of Louisville, Louisville, KY.

Smoke and Endothelial Homeostasis. Christian Heiss, University of Surrey, Guildford, United Kingdom.

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Exposure to Airborne Particulate Matter (PM2.5) and Volatile Pollutants Impacts the Levels of Circulating Angiogenic Cells in Humans. Timothy O’Toole, University of Louisville, Louisville, KY.

The Role of Endothelial Progenitor Cells in Ambient Fine Particulate Matter (PM2.5)-Induced Atherosclerosis. Lung Chi Chen, New York University School of Medicine, Tuxedo Park, NY.

Pulmonary Oxidative Stress and Impaired Growth Factor Signaling: Potential Mechanisms of Air Pollution-Induced Changes in Endothelial Progenitor Cell Homeostasis and Function. Petra Haberzettl, University of Louisville, Louisville, KY.

Panel Discussion/Q&A.

Microphysiological Systems: A New Era in Neurotoxicology?

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Helena Hogberg, Johns Hopkins University, Baltimore, MD; and Benjamin Cappiello, AxoSim, Inc., New Orleans, LA.

Primary Endorser: Neurotoxicology Specialty Section

Other Endorser(s): In Vitro and Alternative Methods Specialty Section; Molecular and Systems Biology Specialty Section

Drug development is a slow, inefficient, and expensive process. The latest estimates from the Tufts Center for the Study of Drug Development show that total cost and time to bring one drug to market is now more than $2.6 billion and is in excess of 10 years. One contributing reason for this attrition rate is that current animal models have limited predictivity for efficacy and toxicity in humans despite their high cost and long study times. As a consequence, 89% of drugs that make it into the clinic still fail in clinical trials and for neurological therapies, the clinical failure rate rises to 94%. Simple monolayer in vitro models have been developed to accelerate testing throughput and to better understand the mechanisms’ underlying effects. In neurological studies, parameters such as neurite outgrowth, cellular area, apoptosis, and electrophysiology are used to evaluate success. However, 2D cell cultures poorly represent human organ function, as they lack the numerous structural and physiological complexities found in vivo. Therefore, it is recognized that more complex systems are needed to improve the success of drug development and toxicity testing. The nervous system is a challenge to model in vitro, as it consists of neurons and glial cells, where intimate cell-cell interactions are critical to development and function. The improved cell-cell interaction in a multi-cellular 3D structure enhances cellular processes such as neurogenesis, synapse formation, and axon myelination. In addition to the improved structure and cell connectivity, these systems have shown increased survival and improved neuronal differentiation compared with traditional monolayer cultures. Furthermore, simple 2D models may not recapitulate exposure of compounds because the nervous system is protected by barriers (blood-brain or retina-barrier), which limit their accessibility. For toxicology, this aspect is of great relevance and several complex 3D models have begun first attempts to integrate barriers in their systems (e.g., a blood-brain barrier [BBB]). The session will discuss the current and future uses of complex neural cell models and microphysiological systems (MPS) in neurotoxicology. The presentations will provide attendees with an in-depth perspective from across government, academia, and industry, and present applications of novel neuroMPS that recapitulate a broad spectrum of the nervous system in toxicology and drug development: BBB, CNS, PNS, and retina. The first presentation will provide a pharmaceutical industry perspective on the need to develop better neural systems due to limitations of current animal models and monolayer cultures. The integration of complex MPS in drug development and toxicity screening will be discussed. The second talk will introduce a microfluidic-based human BBB, which is used to study early neurodevelopment and drug delivery across the barrier. The BBB is a bottleneck in drug development for neurological disorders, as it can block entry into the brain of many chemical agents that would otherwise be potentially useful drugs. The third presentation will focus on a human iPSC 3D neural model consisting of most cell types of the CNS, such as neurons, astrocytes, and oligodendrocytes. It is used for testing compounds for developmental neurotoxicity using transcriptomics and imaging approaches with a primary focus on myelination. Myelination is rarely found in cell cultures; thus, this model represents an important component of the nervous system that can be affected by chemicals. The fourth presentation will describe a 3D Nerve-on-a-Chip platform and its application to peripheral and lower motor neurotoxicity. Peripheral neuropathy is experienced by >40% of patients undergoing chemotherapy and is a common side effect of several therapeutic classes such as antibody-drug conjugates. Additionally, the experience of an MPS model developer working with pharmaceutical companies will be discussed. The final talk will present a Retina-on-a-Chip platform that recapitulates the complex structure and interplay between neuronal cell types and epithelial cells in human retinal tissue and incorporates more than...
eight different cell types all derived from iPSC. This system is used in screening for retinal toxicity and disease modeling. All presenters will discuss advantages, challenges, and current limitations with their approaches. Following the five presentations there will be an interactive panel discussion where audience participation is encouraged.

**Introduction.** Helena Hogberg, Johns Hopkins University, Baltimore, MD.


**A Human BBB Microphysiological System for the Study of Neurotoxicity.** Christopher Hughes, University of California Irvine, and Kino Biosciences, Irvine, CA.

**A Complex Human 3D Neural Cell System to Study Developmental Neurotoxicity.** Helena Hogberg, Johns Hopkins University, Baltimore, MD.

**Nerve-on-a-Chip Platform to Evaluate Peripheral Neuropathy with Clinically Relevant Metrics.** Benjamin Cappiello, AxoSim, Inc., New Orleans, LA.

**Retina-on-a-Chip: Merging Organoid and Organ-on-a-Chip Technology for Complex Multi-Layer Tissue Models.** Peter Loskill, Fraunhofer Institute for Interfacial Engineering and Biotechnology, and Eberhard Karls University Tübingen, Tübingen, Germany.

**Panel Discussion/Q&A.**

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**Order from Chaos: Pattern Recognition in Challenging Human Health Datasets**

**Wednesday, March 13, 1:30 PM to 4:15 PM**

**Chairperson(s):** John Wambaugh, US EPA/NCCT, Research Triangle Park, NC; and Rosemary Zaleski, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ.

**Primary Endorser: Exposure Specialty Section**

**Other Endorser(s):** Risk Assessment Specialty Section; Specialty Section Collaboration and Communication Group

The science of complex systems has demonstrated that while some things about noisy, real-world data are unknowable, certain patterns and structures can emerge from the chaos. Given the increasing complexity of data related to assessing potential risk posed to human health by chemicals, this session is intended to incubate new methodologies for mining “Big Data” to inform functional human health outcomes. Driven by innovations in computational techniques, many problems that were once intractable can now be understood in terms of these recurring patterns. While the areas of research in this session are diverse, there is surprising commonality about the challenges faced by researchers and potential cross-domain applicability of the approaches used to solve the problems. The session begins with an exposomics-based approach to understanding the role that environmental chemical exposures may play in public health outcomes. The workshop continues by addressing metabolomics and novel, non-targeted analysis (NTA) of chemicals in environmental and biological media. NTA analysis generates thousands of chemical features per sample, and each sample contains information about the potential upstream chemical sources or pathways. Algorithms can identify unique feature signatures associated with sample groups, allowing understanding of sample content and history and development of source hypotheses. The session will then explore the world of *in vitro* testing where, among the hundreds of cell lines available, efforts are being made to identify a parsimonious few that explain as much phenotypic variability as possible. The final presenter is from a large, multi-national consulting firm. The presentation will examine prediction of human health outcomes using new analytics techniques to identify environmental toxin “Hot Spots” using Big Data. In all five presentations, identifying patterns in complex data to allow for more informed decision-making. Each presentation will consider: (1) What are the challenges of the system of study? (2) What aspects of that system are unknowable? (3) What patterns emerge for the complexity of the system? (4) What tools are available for identifying these patterns? (5) What are the human health implications for the patterns that can be recognized?

**Introduction.** John Wambaugh, US EPA/NCCT, Research Triangle Park, NC.

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Informatics and Data Analytics to Support Exposome-Based Discovery for Public Health. Jake Chung, Harvard Medical School, Boston, MA.

Finding Patterns within Complex Metabolomics Datasets. Bennard van Ravenzwaay, BASF SE, Ludwigshafen, Germany.


Parsimonious Selection of Cell Lines to Reproduce Phenotypic Variability. Nisha Sipes, NIEHS/NTP, Research Triangle Park, NC.


Panel Discussion/Q&A.

Risk Assessment of Consumer Products and Articles: Critical Considerations and Case Studies for Characterizing and Quantifying Consumer-Relevant Exposures to Chemicals and Nanomaterials

Wednesday, March 13, 1:30 PM to 4:15 PM

Chairperson(s): Susan Felter, Procter & Gamble Company, Mason, OH; and Treye Thomas, Consumer Product Safety Commission, Rockville, MD.

Primary Endorser: Exposure Specialty Section

Other Endorser(s): Nanotoxicology Specialty Section; Risk Assessment Specialty Section

Increasingly, toxicologists are challenged to do risk assessments for consumer products for which the determination of relevant exposure is not straightforward. Quantification of potential exposure from many types of existing and emerging consumer products (e.g., textiles, toys, furniture, diapers, 3D printed products) is still an emerging science and the application of nanomaterials introduces even further challenges. Quantifying exposure that mimics actual and foreseeable consumer use associated with a range of consumer products can require advanced sampling approaches and analytical capability. This raises the question of how we should define what is “reasonably conservative” versus “not relevant” when developing methods. Given the limitations/absence of these capabilities and/or accepted methods, overly conservative methods and assumptions are often used that are not relevant to consumer exposures or represent extreme worst-case use scenarios. The session will provide examples of frameworks and sampling and analytical methods that have been developed to determine exposures from products and articles that are relevant for actual consumer use scenarios. Case studies include the estimation of chemical migration and relevant consumer exposure estimates to engineered nanomaterials along the product value chain, release of silver from nanotechnology-based children’s products, and the potential for migration of any constituents above a TTC-based threshold from a disposable diaper. Factors that are important to consider when developing extraction methods for mimicking consumer use scenarios, including relevant solvents, will be discussed. These data can then be used in robust risk assessments leading to informed decisions on the safety of chemicals in such products under normal usage conditions and improve product safety and risk communication to the public. This session will also consider what exposure data are needed by regulators associated with the new Frank R. Lautenberg Chemical Safety for the 21st Century Act and how end uses of a chemical are considered when estimating the potential for consumer exposure.


Understanding the Changing Exposure and Toxicity Profile of Engineered Nanomaterials from Production to Application. Aaron Erdely, NIOSH, Morgantown, WV.

Estimating the Release of, and Exposure to, Silver from Nanotechnology-Based Consumer Products for Children. Marina Vance, University of Colorado Boulder, Boulder, CO.
This Is Your Teen Brain on Drugs: In Search of Biomarkers Unique to Dependence Toxicity in Adolescents

Wednesday, March 13, 1:30 PM to 4:15 PM

**Chairperson(s):** Abby Li, Exponent Health Science, San Francisco, CA; and Leslie Kwan, George Washington University Public Policy and Public Administration, Washington, DC.

**Primary Endorser: Neurotoxicology Specialty Section**

**Other Endorser(s):** Clinical and Translational Toxicology Specialty Section; Occupational and Public Health Specialty Section

Human variability is an important consideration in toxicology and risk assessment. Significant advances have been made to address differences between the adult and fetus/children or the elderly. In contrast, adolescent teenagers are generally considered to be smaller adults when considering the toxic effects of drugs and chemicals. With the recent legalization of recreational marijuana in several states (California in 2018) and introduction of new electronic nicotine delivery systems (ENDS; e.g., electronic cigarettes, e-hookahs, and other flavorful vapor emitting devices), perceptions around the increased accessibility and decreased risk of harm from cannabis and nicotine use are changing among teens. Historically, these factors have been associated with increased substance use. Emerging evidence from animal and human studies suggests that there are social, psychological, and neurobiological differences between adolescents and adults that increase vulnerability of adolescents to the dependence potential of CNS-active substances. Recently published animal studies suggest that there are behavioral, neurochemical, and/or anatomical changes following adolescent exposures that may be candidates for biomarkers unique to dependence toxicity in adolescents. This session brings together leading experts in the research on dependence toxicity potential of nicotine, cannabis, and/or other illicit drugs during adolescence. The participants will evaluate the strength and limitations of the experimental evidence for increased vulnerability in adolescents compared with adults and the extent to which proposed neurocircuit targets and biological markers are unique to teenage vulnerability for dependence. They will also evaluate whether approaches are generalizable to toxicity testing to screen for effects of chemical and drugs that may increase susceptibility of teenagers to substance use disorders (SUD). Participants will discuss implications of unique patterns of behavioral, neurochemical, and other biomarker changes in adolescents for public health.

Ms. Kwan, a graduate student in Public Policy and Public Administration at George Washington University, who has been involved with research on age of initiation of nicotine on public health outcomes, will briefly introduce the topic and frame the overarching questions for the session. Dr. Eaton will set the stage by presenting recently published (2018) results from one of the most comprehensive studies by the National Academies that he chaired on human health effects of e-cigarettes, including youth initiation. Dr. Levin will begin with a brief introduction on neurochemical and anatomical pathways of addiction followed by presentation of ongoing research on behavioral, anatomic, and signaling pathway markers of nicotine dependence in adolescent and adult rats. Dr. Dow-Edwards will compare and contrast the effects of delta-9-tetrahydrocannabinol (d9THC), the chemical responsible for most of marijuana’s psychological effects, on adolescent brain-behavior relationships with emphasis on male-female differences in alterations of neural circuits mediating these relationships. Dr. Andersen will present a state-of-the-art translational approach showing how a dopamine receptor mediated “switch” underlies age-related periods of drug-induced “protection” or drug-induced vulnerability associated with addiction with the ultimate goal of developing treatments that can be used in teenagers to reduce addiction. The workshop will end in a 40-minute panel discussion led by Dr. Vorhees and Dr. Talpos on the evidence for increased susceptibility and identification of data gaps that will encourage cross-fertilization of ideas for development of novel screens for the potential of chemicals and drugs to increase susceptibility of teenagers to SUD. This session introduces an important new scientific area to SOT; namely, the vulnerability of the adolescent brain to chemical/drug exposure. It will be of interest to a broad audience, including those interested in neurotoxicology, public health, clinical and translational toxicology, drug discovery toxicology, and social implications of this science.

(continued on next page)
Introduction. Leslie Kwan, George Washington University Public Policy and Public Administration, Washington, DC.

Public Health Consequences of E-cigarettes: A Focus on Special Concerns for Youth and Young Adults. David L. Eaton, University of Washington, Seattle, WA.

Rat Models of Adolescent-Onset Nicotine Self-Administration and Persisting Effects of Gestational Nicotine. Edward Levin, Duke University Medical Center, Durham, NC.

Sex-Dependent Effects of Delta-9-Tetrahydrocannabinol on Adolescent Brain-Behavior Relationships. Diana Dow-Edwards, SUNY Downstate Medical Center, Brooklyn, NY.

Translational Approaches for Identifying Biomarkers of Adolescent Risk for Transition to Drug Dependence. Susan Andersen, Harvard Medical School, Belmont, MA.

Panel Discussion with Drs. Charles Vorhees (Cincinnati Children’s Hospital) and John Talpos (US FDA/NCTR). Charles Vorhees, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; and John Talpos, US FDA/NCTR, Jefferson, AR.
Roundtable Session | Wednesday

A Multi-Stakeholder Dialogue on Using Proprietary Modeling Platforms to Support Risk Assessment and Regulatory Decisions

Wednesday, March 13, 4:30 PM to 5:50 PM

Chairperson(s): Angela Hofstra, Syngenta Canada Inc., Guelph, ON, Canada; and Cecilia Tan, US EPA, Research Triangle Park, NC.

Primary Endorser: Specialty Section Collaboration and Communication Group

Other Endorser(s): Biological Modeling Specialty Section; Risk Assessment Specialty Section

Powerful modeling platforms embedded with large databases allow researchers to more efficiently generate robust predictions to evaluate a specific endpoint (e.g., potential toxicity of a compound) even when little data are available. For example, several proprietary physiologically based pharmacokinetic (PBPK) modeling platforms contain extensive demographic, physiologic, and biochemical databases, and simulate internal dosimetry of a compound to assist in extrapolations necessary for estimating human health risks from exposures to environmental chemicals, or evaluating safety and efficacy of drug compounds. Being able to predict human relevance is of keen interest to diverse groups, including academic researchers; developers and producers of chemicals, drugs, and consumer products; regulators; and the general public. Proprietary models have been used extensively in certain regulatory arenas, such as drug development, and are new to others, such as pesticide registration. The primary concern that prevents a regulatory agency from incorporating predictions generated from proprietary modeling platforms into their decision-making processes is the lack of open access to the platforms and underlying models and databases. In this case, regulators, academics, or members of the general public may not be able to replicate the model predictions, or to evaluate the predictive capability of the model within a desired chemical space. This roundtable assembles model developers, model users (e.g., chemical registrants and academics), risk assessors within regulatory agencies, and external stakeholders to share their experience and perspectives on both scientific and nonscientific challenges that limit the use of proprietary modeling platforms in regulatory assessment. While this session will focus the discussions on PBPK modeling platforms, the perspectives are applicable to other modeling platforms. The session will start with brief presentations of different perspectives on the utility of proprietary modeling platforms in both development and safety assessment of chemicals, drugs, or consumer products; processes involved in validating/evaluating model assumptions and predictions; and considerations for protecting intellectual property. Following the presentations, there will be a 50-minute moderated discussion among presenters and audience addressing questions such as, “Is evaluation of a model by the platform developer sufficient to provide confidence in the outputs of a model?” and, “Is access to all modeling platforms and databases used to generate model outputs required to verify the output?” This roundtable gathers parties involved in the use of proprietary models to explore strategies that promote acceptance and use of best science tools in regulatory risk assessment. (Disclaimer: the views expressed in this abstract are those of the authors and do not represent Agency policy or endorsement.)


Proprietary PBPK Modeling: An Academic Perspective. Sami Haddad, University of Montréal, Montréal, QC, Canada.


Panel and Moderated Open Discussion. Marie Fortin, Jazz Pharmaceuticals, Ewing, NJ.
Navigating Turbulent Waters: How to Address Conflict throughout Your Career

Wednesday, March 13, 4:30 PM to 5:50 PM

Chairperson(s): Manushree Bharadwaj, NIEHS, Research Triangle Park, NC; and Brita Kilburg-Basnyat, Covance Inc., Madison, WI.

Primary Endorser: Postdoctoral Assembly

Other Endorser(s): Career Resource and Development Committee; Graduate Student Leadership Committee

In science-based work environments, it can be difficult to navigate personality differences, differing opinions on research directions, project responsibilities, and other work-related situations. Addressing these situations head-on—especially in work environments structured around a rigid hierarchy—can be intimidating to graduate students, postdoctoral trainees, and scientists at all career levels. This session focuses on how to manage and overcome conflict in the workplace to achieve a favorable outcome for all. Throughout this session, attendees will gain insight into how to approach these difficult situations successfully through proper communication, problem-solving, and conflict resolution techniques. To achieve this, we have identified successful leaders from diverse backgrounds, career stages, and workplace environments to discuss the dynamics of the workplace and the skills for navigating challenging situations and coworkers. The session will focus on (1) civil skepticism and fair fighting in the workplace and how to disagree with grace; (2) how to overcome recurring negative judgments and feelings in scientific relationships, in both academia and other scientific organizations; (3) struggles when working with teams or groups; and (4) the importance of providing constructive feedback. These interactive presentations will not only include examples from the presenters’ professional careers, but also present hypothetical situations and discuss appropriate responses to resolve these workplace conflicts and manage tough conversations at all career levels. Thus, these presentations will be highly relevant to all student and postdoctoral attendees that want to improve their conflict management skills, as well as managers, PIs, Directors, and others who regularly interact with and manage a team. This session will enable the audience to learn and implement an essential skill set that will improve professional relationships throughout their careers.

Civil Skepticism and Fair Fighting. Mary Mitchell, The Mitchell Organization, Seattle, WA.

De-energizing Relationships in Academia and Science and How to Manage Them. Dana Dolinoy, University of Michigan School of Public Health, Ann Arbor, MI.


Giving Effective Feedback: Tips for Telling the “Good” or “Bad.” Tammy Collins, NIEHS, Research Triangle Park, NC.
Nerve Agent and Pesticide Poisoning: Best Practice Methodologies for Assessing Long-Term Health Effects

Thursday, March 14, 8:30 AM to 11:15 AM

Chairperson(s): Laurie Roszell, Army Public Health Center, Aberdeen Proving Ground, MD; and David Jett, NIH-Countermeasures Against Chemical Threats (CounterACT) Research Program, Bethesda, MD.

Primary Endorser: Neurotoxicology Specialty Section
Other Endorser(s): Risk Assessment Specialty Section

Exposure to nerve agents, such as chemical warfare agents and organophosphorus pesticides, is a highly topical subject in toxicology, Unfortunately because of their recent use in civilian and military conflict. Nerve agent poisoning after acute high doses is often fatal; however, if life-threatening symptoms can be controlled through medical intervention, many people can survive the acute lethal toxicity. There is an existing body of literature that strongly suggests that nonlethal adverse health effects occur in survivors of acute nerve agent exposure. These “long-term” health effects include neurochemical, neuropathological, and behavioral deficits that occur within days, weeks, or even many years after the exposure. The acute lethal effects of organophosphorus (OP) nerve agents and pesticides have been well described, and data exist for the assessment of hazard and risk. However, understanding and assessing the risk of long-term sequelae is less clear due to the heterogeneity and rigor of human and animal studies. Data on the long-term effects are also important for developing effective medical interventions, since some of the studies describe persistent effects that can significantly reduce quality of life. Often risk assessments are largely retrospective, relying on qualitative data by estimating signs and symptoms at the time of exposure and how long it took for them to develop. The session will present examples of methods for assessing long-term effects in humans and animals following acute exposures to OP nerve agents and pesticides. The session will begin with an overview of the issue, including examples of significant incidents and efforts to retrospectively link exposures to outcomes. The next presenter will describe an NIH/NTP Systematic Review of long-term neurological effects of sarin. This will be followed by a presentation describing a toxidrome-based, subject-matter expert (SME)-informed approach for assessing the risk of long-term health effects following acute exposures to OP nerve agents and pesticides, and the fourth presentation will discuss preclinical models for assessing the neuropathological changes induced by acute intoxication with OPs, and the short- and long-term functional deficits associated with the acute exposures. The session will conclude with a panel discussion.

Overview: Why Do We Need to Understand Long-Term Adverse Health Outcomes following Acute Exposures to Nerve Agents?
Laurie Roszell, Army Public Health Center, Aberdeen Proving Ground, MD.

A Systematic Approach for Assessing Long-Term Effects of Sarin. David Jett, NIH-Countermeasures Against Chemical Threats (CounterACT) Research Program, Bethesda, MD.

A Novel SME-Informed Approach to Assess the Likelihood of Long-Term Injury following Acute Exposures. Kevin Wegman, Battelle Memorial Institute, Columbus, OH.

Preclinical Models to Assess Long-Term Neurological Sequelae of Acute Intoxication with Organophosphate Nerve Agents. Pamela Lein, University of California Davis, Davis, CA.

Panel Discussion/Q&A. Laurie Roszell, Army Public Health Center, Aberdeen Proving Ground, MD.
New Mechanistic Insights into Causes and Outcomes of Epigenetic Dysregulation by Carcinogenic Metals

Thursday, March 14, 8:30 AM to 11:15 AM

Chairperson(s): Chunyuan Jin, New York University School of Medicine, New York, NY; and J. Christopher States, University of Louisville, Louisville, KY.

Primary Endorser: Metals Specialty Section

Other Endorser(s): Carcinogenesis Specialty Section; Mechanisms Specialty Section

Metal contamination impacts hundreds of millions of people in the world. Metal exposure can cause human diseases including cancer. Carcinogenic metals are in general considered to be weak mutagens, suggesting that mechanisms other than genetic changes play major roles in metal-induced carcinogenesis. Epigenetic mechanisms have recently emerged as important players in response to metal exposure. Epigenetic regulations include DNA methylation, histone modifications, microRNA expression, incorporation of histone variants, and nucleosome positioning and chromatin accessibility. Most studies of metal-induced epigenetic dysregulation have focused on changes in epigenetic profiles in terms of DNA methylation, global histone modifications, and microRNA expression. However, mechanisms that control these changes and consequences of these changes are not well examined. Moreover, little is known about genome-wide changes in chromatin accessibility and assembly of variant histones following metal exposures. While high-throughput sequencing technologies such as RNA-seq, ChIP-seq, and Methyl-seq have recently been applied for studies of metal-induced epigenetic regulation, newer technologies such as ATAC (Assay for Transposase-Accessible Chromatin) have not been as widely used in studies involving metal toxicity. This symposium aims to highlight recent advances in environmental epigenetics, focusing on new molecular insights into epigenetic dysregulation by metal exposure and on the use of cutting-edge new technologies in studies of environmental epigenetics. The first speaker identifies a set of differentially methylated genes in exfoliated urothelial cells (EUCs) in a cohort study. Promoter analysis shows that the arsenic-associated genes are enriched for the binding sites of common transcription factors known to play roles in carcinogenesis. The second speaker demonstrates hsa-miR-186 induction by arsenic exposure and how overexpression of hsa-miR-186 induces chromosomal instability in keratinocytes, providing a mechanism for induction of aneuploidy by arsenic exposure. In the third presentation, the speaker presents the changes in the levels of histone variants during arsenic-induced epithelial to mesenchymal transition (EMT) as well as a possible mechanism that causes differential methylation at specific genomic loci in arsenic-transformed cells. The fourth speaker uses cutting-edge new technologies such as DANPOS (Dynamic Analysis of Nucleosome Positioning and Occupancy by Sequencing) and ATAC (Assay for Transposase-Accessible Chromatin) to show how nucleosome positioning and chromatin accessibility are changed by chromium exposure. The fifth speaker uses an animal model to demonstrate polyadenylation of canonical histone mRNAs following nickel and arsenic exposures. In vitro studies further reveal that increase in polyadenylated canonical histone mRNAs disrupts nucleosome assembly of histone variants at active promoters. In summary, this symposium will provide attendees mechanistic and new aspects of epigenetic dysregulation by metal exposure and their implications in metal-induced carcinogenesis, as well as better understanding of new approaches for studying chromatin landscape following environmental exposures. Potential use of these epigenetic changes in cancer risk assessment will be discussed.

Introduction. Chunyuan Jin, New York University School of Medicine, New York, NY.

Links between Arsenic-Associated DNA Methylation and Bladder Cancer. Julia Rager, University of North Carolina at Chapel Hill, Chapel Hill, NC.

hsa-miR-186 Overexpression Induces Aneuploidy in Human Keratinocytes. J. Christopher States, University of Louisville, Louisville, KY.

Chromatin Structural Changes and Function in Inorganic Arsenic-Mediated Cellular Transformation. Yvonne Fondufe-Mittendorf, University of Kentucky, Lexington, KY.

Hexavalent Chromium Disrupts Chromatin Architecture. Andrew VonHandorf, University of Cincinnati College of Medicine, Cincinnati, OH.

Polyadenylation of Canonical Histone mRNA by Carcinogenic Metals Nickel and Arsenic Disrupts Chromatin Homeostasis and Is Highly Carcinogenic. Max Costa, New York University School of Medicine, New York, NY.
Exposure to toxicants during critical windows of in utero or early postnatal development can alter coordinated differentiation and growth programs, resulting in significant impacts on the trajectory of development and adverse health outcomes in later life. Recently, it has been recognized that the preconception window of exposure is an overlooked critical period during which toxicants can alter the processes required for successful gametogenesis. Gametogenesis, like early development, requires precisely timed cell division and differentiation to produce mature gametes with appropriate genetic and epigenetic contents, organelles, and RNAs necessary for fertilization and development. This session will explore how toxicants adversely affect gametogenesis, impair gamete quality, and contribute to health and disease states in offspring. The session will begin with an overview presentation on the background and rationale for this research area, after which speakers will discuss experiments demonstrating preconception exposure effects of a range of compounds, including ethylene glycol monomethyl ether, phthalates, perfluorinated alkyl substances, and mitochondrial toxicants, on oogenesis and spermatogenesis in rats, mice, zebrafish, C. elegans, and humans. The goal of this session will be to answer the following questions: How do toxicant exposures adversely alter gametogenesis; how can those effects be measured; and what are the impacts on offspring health outcomes? These presentations will demonstrate that the preconception window of exposure is a sensitive window for the development of health and disease states in later life, with potentially broad ramifications for understanding the mechanisms of toxicity contributing to transgenerational effects and for regulatory testing of reproductive toxicants.

Introduction. Daniel Spade, Brown University, Providence, RI.

The Preconception Exposure Window and Health of the Offspring. Thaddeus Schug, NIEHS, Durham, NC.

Testicular Toxicants as Modifiers of Sperm Epigenetic States: Ethylene Glycol Monomethyl Ether as a Case Study. Angela Stermer, Brown University, Providence, RI.

Male Preconception Phthalates on Sperm Epigenetics and Early-Life Development. J. Richard Pilsner, University of Massachusetts Amherst, Amherst, MA.

Maternal Preconception Exposure to PFOS Affects Nutrient Content of Oocytes and Later-Life Pancreas Development. Karilyn Sant, San Diego State University, San Diego, CA.

Does Exposure to Mitochondrial Toxicants during Germ Cell Development Result in Lifelong Alterations in Mitochondrial Function Mediated by Epigenetic Changes? Joel Meyer, Duke University, Durham, NC.

Panel Discussion/Q&A.
Potential Alternatives to Systematic Review: Evidence Maps and Scoping Reviews

Thursday, March 14, 8:30 AM to 11:15 AM

Chairperson(s): Brandiese Beverly, NIEHS/NTP, Research Triangle Park, NC; and Johanna Rochester, The Endocrine Disruption Exchange, Eckert, CO.

Primary Endorser: Risk Assessment Specialty Section

Other Endorser(s): Regulatory and Safety Evaluation Specialty Section

Systematic reviews, with their comprehensive, transparent, and repeatable protocols, are rapidly becoming the gold standard for using existing literature to assess environmental health questions. However, there are instances when a full systematic review may not be feasible or necessary to address particular questions or to make decisions (e.g., for funding, future research, or regulation). Alternatively, there are less labor-intensive ways, using systematic methodologies, to answer questions in environmental health that do not require (or are premature for) an exhaustive systematic review. Scoping reviews and evidence maps are systematic, transparent assessments that may be better suited for some research questions. These intermediate alternative products can be performed more quickly and are often used to inform systematic reviews (usually in the initial steps of problem formulation and development), and can also serve as publishable stand-alone products. Two major challenges of conducting systematic review for decision-making are the time and resources needed to complete the review. On average, systematic reviews can take more than 1,000 hours to complete and can cost over $100,000. Further, by the time a systematic review is published, those data can be outdated, and thus perhaps not useful for rapid decision-making. Systematic evidence maps represent a process for categorizing literature to rapidly map key concepts, types of evidence, and data gaps related to a defined research area, and can include an interactive visualization of the relevant data. These maps are useful in identifying characteristics of studies that might facilitate decision-making for a particular research question, such as evidence stream, exposure information, dose ranges, and major health effects. Systematic evidence maps can be stand-alone products, can inform other intermediate products (e.g., scoping reports), or can be used within a systematic review as part of problem formulation efforts. Scoping reports can take the information from a systematic evidence map further and can begin synthesizing results to serve as a stand-alone product or can inform systematic reviews, for example, by narrowing in on a specific endpoint or chemical for further review. Presenters will use specific case studies to introduce the concepts of systematic reviews, evidence maps, and scoping reports, and highlight their utility and limitations/challenges in addressing certain research questions or decision-making. The session will begin with an overview of basic systematic review principles and how they are used in environmental health. The strengths and limitations of systematic reviews will be discussed, followed by an introduction to systematic maps and scoping reports, and their utility in addressing the challenges of conducting systematic reviews. Following the introduction, there will be four case examples of a systematic review, scoping report, and evidence maps. The presentations will detail the research question(s) addressed by use of these systematic products as well as tools that could potentially facilitate the generation of the reviews/reports where applicable. The advantages and limitations for each review or report type will be discussed, as well as how the product was used for decision-making. The session concludes with a panel discussion to provide thoughts on the utility, advantages, disadvantages, and challenges of these reviews/reports within the systematic review spectrum. The panel will discuss how advances in automation and interest in publication can contribute to the uptake and usability of these products, and hopefully serve to streamline decision-making in environmental health.

Brief Overview and Introduction to Systematic Review and Related Products. Brandiese Beverly, NIEHS/NTP, Research Triangle Park, NC.

Rigor and Resources for Systematic Reviews in Toxicology: Case Study Applications in Food Safety, Consumer Product Safety, and Environmental Health Risk Assessment. Daniele Wikoff, ToxStrategies, Inc., Asheville, NC.

Systematic Mapping as a Tool for Regulatory Risk Assessment in Environmental Health: Tetrabromobisphenol A (TBBPA) as a Proof of Concept. Taylor Harrison, Lancaster University, Lancaster, United Kingdom.

Illustrating Fit for Purpose in Systematic Evidence Maps: Case Study Mapping of the Evidence of Transgenerational Health Effects. Vickie Walker, NIEHS/NTP, Research Triangle Park, NC.

(continued on next page)
Use of Adverse Outcome Pathways to Design Nonanimal Testing Strategies for Assessing Inhalation Toxicity

Thursday, March 14, 8:30 AM to 11:15 AM

Chairperson(s): Amy Clippinger, PETA International Science Consortium Ltd., Norfolk, VA; and Robert Landsiedel, BASF SE, Ludwigshafen, Germany.

Primary Endorser: In Vitro and Alternative Methods Specialty Section
Other Endorser(s): Mechanisms Specialty Section; Inhalation and Respiratory Specialty Section

Inhalation is a major route of human exposure to airborne substances. This may cause portal-of-entry effects in the respiratory tract and can also lead to systemic uptake and subsequent effects. Several adverse outcomes in the airways are known, including acute lethal effects and chronic diseases. Adverse outcome pathways (AOPs) can be used to describe the mechanism through which a substance causes toxicity and inform the selection of in silico and in vitro methods to include in integrated approaches to testing and assessment (IATAs). In this session, speakers from government, industry, academia, and NGOs will discuss mechanisms relevant to adverse outcomes following inhalation exposure, including lung inflammation and irritation, and the in silico and in vitro methods that can be used to assess key events. Case study examples showing how AOPs have been used to design testing approaches that inform risk assessment decisions will be highlighted. The presentations will discuss the implementation of IATAs that combine the use of existing data with dosimetry considerations, physicochemical property information, in vitro, and computational approaches to fulfill current data needs. Specifically, the first presentation will set the stage for the remaining talks by highlighting the importance of and providing an example of material characterization and dosimetry considerations that must proceed in vitro testing. The second talk will describe a computational and in vitro approach based on an AOP for squamous metaplasia that has been submitted to the US EPA for the registration of a fungicide. The third talk will discuss an integrated approach for testing reactive gases using an AOP for ILC-2-mediated respiratory remodeling to inform assay selection and interpretation of study results. The fourth presentation will detail the use of precision-cut lung slices to query key events in an AOP for chronic obstructive pulmonary disease. The final talk will present a regulatory perspective on processes in place to accept alternative approaches for inhalation toxicity testing, the use of mechanistic and exposure information to facilitate regulatory acceptance, and remaining hurdles.

Introduction. Robert Landsiedel, BASF SE, Ludwigshafen, Germany.


Source-to-Outcome: In Vitro Airway Epithelium Models and Inhalation Dosimetry Modeling to Improve Human Health Risk Assessment. Paul Hinderliter, Syngenta Crop Protection, Greensboro, NC.


Ex Vivo Precision-Cut Lung Slices: Highlighting Key Chronic Obstructive Pulmonary Disease (COPD) Events for Adverse Outcome Pathways. Holger Behrsing, Institute for In Vitro Sciences, Inc., Gaithersburg, MD.


Panel Discussion/Q&A.
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