

# Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects

## Details

**Location:** Sheraton Chapel Hill, 1 Europa Dr., Chapel Hill, NC 27517

**Audience:** The audience for this workshop will consist of invited participants and registered observers. The participants were invited based on their expertise and will actively participate in the breakout session discussions. Observers will be able to provide written comments during the meeting and provide input during the question and answer periods. Time-permitting and at the discretion of the chairpersons, observers will also be able to participate in breakout session discussions.

**Meeting support:** Support for this workshop in the form of scientific writing by Marisa Naujokas, Ph.D., and logistical coordination by Kerri Moran, CMP, CGMP, is provided by MDB, Inc. through an NIEHS contract.

**Registration:** The registration desk will open at 7:30 am each morning and will be available throughout the day.

**Lunch:** Box lunches will be available for purchase at a cost of approximately \$10. Please fill out box lunch selection at the meeting registration desk by 10:30 am each morning.

## Agenda

### Day 1 – Monday, September 26, 2011

Day 1 of the workshop will begin with a panel of presentations that will provide overviews of relevant areas (epidemiology, statistics, biology, exposure, and risk assessment) within mixtures research. The speakers will provide a background on mixtures from their discipline's perspective, including knowledge gaps and future directions of mixtures research. These presentations are not meant to be comprehensive, but to stimulate thought, conversation, and to introduce the unique challenges faced by each of the disciplines.

**8:30-8:45 – Welcome – John Bucher, PhD, Director of the Division of the National Toxicology Program**

**8:45-9:00 – Introduction to Workshop – Cynthia Rider, PhD, Toxicologist, DNTP (Co-Organizer)**

### Day 1 Plenary Session: State of the Science of Mixtures

**Chairperson: Cynthia Rider, PhD**

**9:00-9:25 – Risk Assessment Overview – Glenn Rice, PhD (US EPA/NCEA)**

**Title: Chemical Mixtures: What Dose-Response Analysts Really Want**

Glenn Rice is a leader in the field of cumulative risk assessment and has contributed his expertise to many assessments of complex mixtures (e.g. PAHs, drinking water contaminants) and has knowledge of the various approaches used by the US EPA. He has provided expertise and direction to the EPA's mixtures program.

**9:25-9:50 – Exposure Science Overview – Paul Price, MS (Dow)****Title: What are the Combinations of Chemicals to Which We are Exposed, How can We Identify the Relevant Combinations, and Why is this Important?**

Paul Price is an authority on developing models to assess exposure to multiple chemicals. He understands the data required for accurately predicting human exposure. He is currently interested in identifying the constituents responsible for the observed effects of complex mixtures.

**9:50-10:15 – Biology/Toxicology Overview – L. Earl Gray, PhD (US EPA/NHEERL)****Title: A Biological/Toxicological Perspective on Mixtures Research**

Earl Gray has been instrumental in advocating the biological perspective in mixtures research, shifting focus from mechanisms of individual chemicals to target pathways and tissues affected by multiple chemicals. His work on mixtures that target androgen signaling has been extensively used by regulatory agencies in deciding how to group chemicals for cumulative risk assessment.

**10:15-10:30 – Break****10:30-10:55 – Epidemiology Overview– David Christiani, MD (Harvard University, School of Public Health)****Title: Epidemiologic approaches to the study of mixed exposures**

David Christiani is a world renowned epidemiologist, and he will provide a description of the challenges associated with linking multiple exposures to human disease. He is currently conducting studies on metal mixtures.

**10:55-11:20 – Statistics Overview – Chris Gennings, PhD (Virginia Commonwealth University)****Title: Empirical Whole Mixture Approach for Risk Evaluation: Combining Exposure and Mixtures Toxicity Data**

Chris Gennings is an expert in the statistical approaches available for predicting the toxicity of chemical mixtures and for identifying chemical interactions by determining significant deviations from additivity. She has participated in numerous cross-discipline collaborations to assess the effects of a diverse array of mixtures and she has served as a mixtures expert on multiple advisory panels (e.g. NAS phthalate panel, EPA PAH panel).

**11:20-11:35 – Charge for Day 1 Breakout Session****Chairperson: Danielle Carlin, PhD, Program Administrator, DERT (Co-Organizer)**

This breakout session will provide the participants the opportunity to discuss current challenges in mixtures research within their disciplines. Participants will be divided into five breakout groups according to their specialty (biology/toxicology, epidemiology, statistics, exposure science, risk assessment). They will be asked to develop a comprehensive, discipline-specific list of knowledge gaps in mixtures research. The discussion within these breakout groups will be based on the Request for Information (RFI) (active March-April, 2011; <http://ntp.niehs.nih.gov/go/rfimix>), and the questions will be provided to each group:

1. What are the underlying scientific knowledge gaps for assessing the effects of mixtures on human health?
2. What are the scientific issues encountered in performing risk assessments of mixtures that can be addressed by new research?

3. What types of scientific data (e.g., mechanistic, epidemiological, etc.) are needed to address these underlying knowledge gaps?
4. What are the new technologies and innovative approaches that could be leveraged to address these underlying knowledge gaps?

We will also ask that the participants attempt to prioritize the issues based on importance. Each chairperson will provide a 15-minute presentation describing the output from the discussion within their groups. In addition, NIEHS staff will provide the results gathered previously from the RFI (March-April, 2011).

**11:35-12:30 – Day 1 Breakout Session**

**12:30-1:30 – Lunch (box lunch available for purchase)**

**1:30-3:15 – Day 1 Breakout Session (continued) and development of presentations**

**3:15-3:30 – Break**

**3:30-5:30 – Report back/discussion**

**Chairperson: Mike DeVito, PhD, Senior Toxicologist, DNTP**

- 3:30-3:45 – Epidemiology Group Presentation (Elizabeth Whelan, PhD)
- 3:45-4:00 – Risk Assessment Group Presentation (Moiz Mumtaz, PhD)
- 4:00-4:15 – Statistics Group Presentation (Paul Feder, PhD)
- 4:15-4:30 – Biology/Toxicology Group Presentation (Raymond Yang, PhD)
- 4:30-4:45 – Exposure Science Group Presentation (Antonia Calafat, PhD)
- 4:45-5:00 – Presentation of RFI Responses (Cynthia Rider, PhD)
- 5:00-5:30 – Questions/Discussion

**Post Day One**

**6:00-8:00 – Working dinner for DERT/DNTP/DIR, speakers/chairpersons (tentative location: Shula's 347 Grill)**

A working dinner consisting of members of DERT, DNTP, DIR, speakers, and chairpersons will meet to discuss results from Day 1 activities.

---

**Day 2 – Tuesday, September 27, 2011**

Day 2 will consist of presentations that describe tools or approaches that are relatively new and could contribute to integrating disciplines and advancing the field of mixtures research.

**8:30-8:45 Introduction to Day 2 – Linda Birnbaum, PhD, DABT, ATS, Director of NIEHS**

**Day 2 Plenary Session: Tools for the Future of Mixtures Research**

**Chairperson: Danielle Carlin, PhD, Program Administrator, DERT (Co-Organizer)**

**8:45-9:05 – Paige Tolbert, PhD (Emory University)****Title: Developing Strategies to Advance Multi-Pollutant Epidemiologic Research**

Paige Tolbert is the Center Director for *The Southeastern Center for Air Pollution and Epidemiology: Multiscale Measurements and Modeling of Mixtures*. She will discuss the innovative approaches for modeling air pollution exposure and measuring health outcomes proposed in projects at the Center.

**9:05-9:25 – Andreas Kortenkamp, PhD (University of London)****Title: Mixture Effects and Epidemiology – The Need for Unbiased Approaches to Exposure Assessment**

Andreas Kortenkamp is a leading expert in mixtures research in Europe and is a lead author on the *State of the Art Report on Mixture Toxicity*. He is currently interested in promoting an approach for integrating epidemiological and animal research in order to decrease uncertainty associated with animal-only mixtures research.

**9:25-9:45 – Chirag Patel, PhD (Stanford University)****Title: Environment-Wide Association Studies: Creating Data-Driven Hypotheses Regarding Environmental Correlates to Common Disease on a Population Scale**

Chirag Patel is a junior investigator and up-and-coming leader in the field of translational bioinformatics. He has been developing methods to conduct environmental-wide association studies (EWAS) and conducting analysis of the expansive amount of “omics” data available in the public domain to answer complex questions on human diseases and mixtures.

**9:45-10:00 – Break****10:00-10:15 – Charge for Day 2 Breakout Session****Chairperson: Claudia Thompson, PhD, Branch Chief, DERT**

Participants will be placed in multidisciplinary groups such that there will be representative experts from each discipline within every group. Each group will be provided with a specific topic (see brief descriptions of topics below) and several scenarios to facilitate discussion of approaches for integrating research across disciplines, research strategies to address the topic, and potential challenges in conducting research on this topic. Detailed information for the topics listed below can be found in the Supporting Document (see website). **Note:** The scenarios associated with each topic are provided ONLY to stimulate discussion. Alternatively, breakout groups can propose other scenarios for discussion that are relevant to the topic.

**Group 1 Topic – Modeling Mixture Toxicity: Constraints of Extrapolation**

What are recommended research approaches to overcome the key challenges to the application of predictive models of mixture toxicity (e.g. dose addition, sufficient similarity of complex mixtures, or alternative models)?

**Group 2 Topic – Exposure Assessment: Making Sense of Biomonitoring Data**

How can we use exposure data (e.g. the Exposure Biology Program, NHANES, and the exposome) in designing toxicology and epidemiology studies to better understand the contribution of environmental exposures to human disease?

**Group 3 Topic – Epidemiology: Reconciling Epidemiological and Toxicological Approaches to Mixtures**

What are suggested research strategies that incorporate lessons from both epidemiology and toxicology to increase our understanding of the role of environmentally-relevant mixtures in human disease?

**Group 4 Topic – Chemical Interactions: Predicting the Unpredictable**

What types of in vitro to in vivo approaches are needed to screen chemicals for potential interactions and how can they best be applied to provide biologically-meaningful information?

**Group 5 Topic – Mixtures across Time**

What types of research approaches are required to elucidate principles of both mixture exposures and associated health effects across time?

**10:15-12:00 – Day 2 Breakout Session**

**12:00-1:00 – Lunch (box lunch available for purchase)**

**1:00-2:00 – Day 2 Breakout Session (continued) and development of presentations**

**2:00-2:15 – Break**

**2:15-4:00 – Report back/discussion**

**Chairperson: Claudia Thompson, PhD, Branch Chief, DERT**

2:15-2:30 – Topic 1: Mixture Modeling Presentation (Richard Hertzberg, PhD)

2:30-2:45 – Topic 2: Exposure Assessment Presentation (Julia Gohlke, PhD)

2:45-3:00 – Topic 3: Epidemiology and Toxicology Presentation (Tom Webster, PhD)

3:00-3:15 – Topic 4: Chemical Interactions Presentation (Deborah Cory-Slechta, PhD)

3:15-3:30 – Topic 5: Temporal Mixtures Presentation (Dana Barr, PhD)

3:30-4:00 – Questions and Discussion

**4:00-4:15 – Closing remarks – Richard Woychik, PhD, Deputy Director of NIEHS**