Day 1 Breakout Session: Biology/Toxicology

Chairperson: Raymond Yang, PhD
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Underlying Scientific Knowledge Gaps

- Need to understand the utility and limitations of in vitro (including HTS) - verification needed with in vivo systems
- Need for modeling across different **physiological systems** (e.g. immuno, neuro) and **species**
- Need to understand how naturally occurring chemicals (e.g. plant estrogens, metal mixtures) may interact with man-made chemicals (e.g. drugs)
- Need for integration of systems biology with computer modeling/simulations
- Mixture testing strategies should be based on predictive/systems biology approaches to fill data needs

Underlying Scientific Knowledge Gaps (continued)

- Need to understand how collection/concentration of samples affects the biological response to the mixture
- Need to calculate accurate individual exposure data (i.e. may vary with gender, activity, age, race)
- Nanoparticle toxicology

Issues Encountered in Performing Risk Assessment of Mixtures

- Need to understand appropriate experimental design
- Dose-response extrapolation relating to humans and experimental models
- In vitro to in vivo validation required prior to application of in vitro data to risk assessment
- Need to know the underlying dose-response curves of the components of the mixtures
- What is the impact of the biological extrapolation from the selected model (current models may not capture biological relevance)
- Need to study mixture and toxicological thresholds

Types of Scientific Data Required

- Define exposure scenarios
- Relevant target tissues
- Use lower organisms (e.g. zebrafish) to bridge conserved pathways
- Use bioinformatics to back-extrapolate in vivo to in vitro or to build HTS signatures
- Chemometrics/Toxicometrics (component analysis versus whole mixtures)
- Life cycle analysis of the chemical mixture (e.g. remove Pb from gasoline and replace with MTBE)
- Integrating mechanism of action into epidemiological studies

Technologies and Innovative Approaches

- Computational toxicology/ HTS/iterative approaches/ bioinformatics
- New modeling approaches and systems biology
- Need to determine mechanism of action and apply to epidemiological studies
- Use and learn from ecological methods/approaches
- Use of lower organisms to answer questions in humans (pathways conserved)
- New study designs to look at low-dose effect region
- New and better human exposure assessments

Technologies and Innovative Approaches (continued)

- Engineers, biologists, and others working together to prepare and analyze samples (i.e. doses and biological samples)
- Explore other biological systems that are not commonly assessed in mixtures studies (e.g. immunological, cardiological, pulmonary, neurological etc.)
- Economic analysis of relevant mixtures

Discussants

Mamta Behl (rapporteur)
Chad Blystone
Christopher Borgert
Danielle Carlin
Deborah Cory-Slechta
Stephania Cormier
Kevin Crofton
Paul Foster
Julia Gohlke
L. Earl Gray
Jerry Heindel
Marike Kolossa-Gehring
Andreas Kortenkamp
Susan Schantz
Jane Ellen Simmons
Raymond Yang (chairperson)