Challenges and Approaches for Mixtures in Risk Assessment

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Introduction

• Increasing pressure to more routinely conduct cumulative risk assessment for exposures to multiple chemicals

• Challenges in identifying which agents should be combined
  – Common mode of action?
  – Common pathway?
  – Do co-exposures occur?
Recent NAS Reports and Recommendations

• Phthalates and Cumulative Risk Assessment
  – Suggests that cumulative assessments be considered for agents that produce the same types of health outcomes

• Science and Decisions (silver book)
  – Recommends combining chemical and non-chemical stressors, increase use of biomonitoring data
Basis for the Phthalates Report Recommendation

- Phthalates inhibit testosterone synthesis in the fetus, affecting male reproductive development
- Effects are comparable to those produced by androgen receptor antagonist, a different mechanism
Testosterone: Mechanism of Action

Androgen-responsive genes

Transporters  Extracellular matrix  Receptors  Enzymes

Cellular Response

Specific mRNAs (Up- or Down-regulated)
Biotechnology to Identify Common MOA or Pathways

- Microarrays/toxicogenomics
- High-throughput screening
Time and dose response of gene expression changes induced by chemical exposure
### Chemical Comparison

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<th>Chemicals comparison / # of common Activities</th>
<th>All 10 Chemicals</th>
<th>DEHP &amp; DINP</th>
<th>Acet &amp; DEHP</th>
<th>Acet &amp; DINP</th>
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**Common biological activity:** hepatotoxicity, but closer structural analogs show higher degree of similarity
ToxCast

• Program to test high number of chemicals in high-throughput mode
• 500+ assays
  – Biochemical
    • Receptor binding
    • Enzyme inhibition
  – Cellular
  – “pathway”
Grouping the ToxCast assays by disease/ pathway

Pathways & Diseases In Vivo
Chemical, biological and statistical
ToxPi: looking for signals of biological activity

\[
\text{ToxPi} = \sum_{i=1}^{I} w_i \cdot \text{assay}_i + \sum_{c=1}^{C} w_c \cdot \text{chemProp}_c + \sum_{p=1}^{P} w_p \cdot \text{pathway}_p
\]

\text{ToxPi} = f(\text{in vitro assays} + \text{chemical properties} + \text{pathways})
The Contribution of Biomonitoring to Cumulative Assessment

• To which chemicals are we concurrently exposed?
• At what concentration (especially in relation to RfD)?
Workshop Overview

• Concepts and grounding
• Emerging science
• Case studies
• Discussions of research needs and regulatory implications
• Synthesis of scientific disciplines in an attempt to find novel approaches to a persistent question