Mixtures: Past and Future at NIEHS

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Recent Events bring Mixed Exposures into Focus

• Environmental Disasters
  – Gulf oil spill
  – Flooding along the East and Southeast Coasts
  – Earthquake and Fukushima Daiichi nuclear disaster

• Regulatory Efforts
  – PAH relative potency factor approach and SAB recommendations
  – Office of Pesticides Program Cumulative Risk Assessments
    • Organophosphates
    • N-methylcarbamates
    • Pyrethroids
  – Phthalates Cumulative Risk
    • NAS report recommendations
Recent Activities in Mixtures Research

• Multipollutant Science and Risk Analysis Workshop: Addressing Multiple Pollutants in the NAAQS Review Process (February 2011)

• SOT 50th Anniversary Meeting (March 2011)
  – CE course, Incorporating Non-chemical Stressors into Cumulative Risk Assessment Workshop, Symposium on Mixtures and Reproductive Toxicology

• NAS Meeting: Mixtures and Cumulative Risk Assessment: New Approaches Using the Latest Science and Thinking about Pathways (July 2011)

• International Toxicology of Mixtures Conference (October 2011)
Funding Mechanisms to Support Mixtures Research at NIEHS

- RFA ES-98-002: Chemical Mixtures In Environmental Health
- Superfund Research Program (SRP) (P42)
- Outstanding New Environmental Scientist Award (ONES) (R01)
- NIH National Research Service Award Institutional Research Training Grants (T32)
- Mentored Clinical Scientist Research Career Development Award (K08)
- Investigator Initiated/Parent Announcements
  - R01, R03, R21
- Academic Research Enhancement Award (R15)
- NIH Pathway to Independence (PI) Award (K99/R00)
- Small Business Innovation Research Grant Applications (SBIR) (R43)
**Chemical Mixture Types:**
- Air Pollution and PM
- PCBs
- PBDEs
- Metals
- Pesticides
- Organochlorines
- PAHs
- Chlorinated and Non-chlorinated Chemicals
- Xenoestrogens

**Research Study Types:**
- Epidemiology
- Mechanistic
- Statistical Analysis
- Developmental
- Exposure
- Mathematical modeling
- Remediation
- Fate and Transport

**Health Outcomes:**
- Cognitive and neurodevelopmental changes
- Reproductive effects
- Mortality and hospital admissions
- Oxidative stress
- Immunological effects
- Genetic and epigenetic alternations
- Disruption of transition metal homeostasis
The Gulf Long-term Follow-up (GuLF) Study

Objectives:

• Assess health effects associated with oil spill clean-up following Deepwater Horizon disaster
  – Physiologic/biologic effects from oil
  – Effects due to disaster-related stress

• Investigate biomarkers of adverse biological effects

• Create a resource for future collaborative research

www.nihgulfstudy.org
www.niehs.nih.gov
Mixtures Research  
Division of the National Toxicology Program

• Whole Mixtures Testing
  – Herbals program (aloe vera, ginkgo, green tea, etc.)
  – Flame retardants (Firemaster FF-1)
  – Marine diesel fuel

• Defined Mixtures
  – 25 groundwater contaminants
  – AIDS drugs used in combination therapies

• Component Based Approaches
  – Dioxin toxic equivalency factor study
New Tools for Mixtures Toxicology

• Toxicology in the 21st Century – HTS, omics
• Human Genome for Gene-Environment Interactions
• Exposure Sciences and the Exposome
• Computational Sciences – Taking advantage of the available data and computational tools
Conceptual Shift
Activation of Toxicity Pathway

Exposure

Tissue Dose

Biologic Interaction

Perturbation

Normal Biologic Function

Early Cellular Changes

Cell Injury

Adaptive Stress Responses

Morbidity and Mortality

Biologic Inputs

NAS Report, 2007
Toxicity Testing in the 21st Century

• Advancing Technology
  – In vitro screening
    • Human tissues more readily available
    • Increases in through-put
      – From 10’s to 100,000 chemicals/year/assay
  – Omics
    • Genomics, Proteomics, Metabolomics
      – From single endpoints to high content data (10’s of endpoints to 10,000’s)
  – Bioinformatic advances and challenges
    • How do we use all this high content data?
      – Development of databases linking genomic signatures with pathologies
      – Development of predictive signatures of pathological and toxicological concerns
The Genes, Environment, and Health Initiative

Genetic Susceptibility - Linking Exposure to Disease

**Exposure Biology Program**
- Identify genetic variants in animal models, develop technology and biomarkers
  - Diet
  - Physical Activity
  - Environmental Exposures
  - Psychosocial Stress and Addictive Substances

**Human Genetics Program**
- Identify genetic variants
  - GWA Studies
  - Data Analysis
  - Replication
  - Sequencing
  - Database
  - Function
  - Translation

GxE
- Genetics
- Epigenetics
- Environment
- Time
Exposure data

• New and more sensitive analytical techniques are constantly being developed (e.g. improved analytical chemistry and development of tools through the Exposure Biology Program)

• There are more comprehensive databases on human exposures to environmental chemicals than ever before
  – NHANES
  – Child Health Study
  – GuLF Study
  – California Biomonitoring Program

• How do we harness the power of this exposure data and link it to human health outcomes?
Exposome

- Total exposure from internal and external sources that impacts the internal chemical environment

- Takes advantage of new analytical chemistry and metabolomic methodologies

- Development of the Exposome may provide insight into new biomarkers of exposure and disease

S M Rappaport, M T Smith Science 2010;330:460-461
Moving Forward in Mixtures Toxicology

• Present Paradigm
  – One route
  – One source
  – One chemical class

• Future Paradigm
  – Total Exposure
    • All routes
    • All sources
    • All chemicals – endogenous and exogenous
    • All stressors – chemicals, nutrition, psychosocial, lifestyle, infectious diseases
ADVANCING RESEARCH ON MIXTURES:
New Perspectives and Approaches for Predicting Adverse Human Health Effects