ADVANCING RESEARCH ON MIXTURES:
New Perspectives and Approaches for Predicting Adverse Human Health Effects

Mixtures: Past and Future at NIEHS

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NIEHS
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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

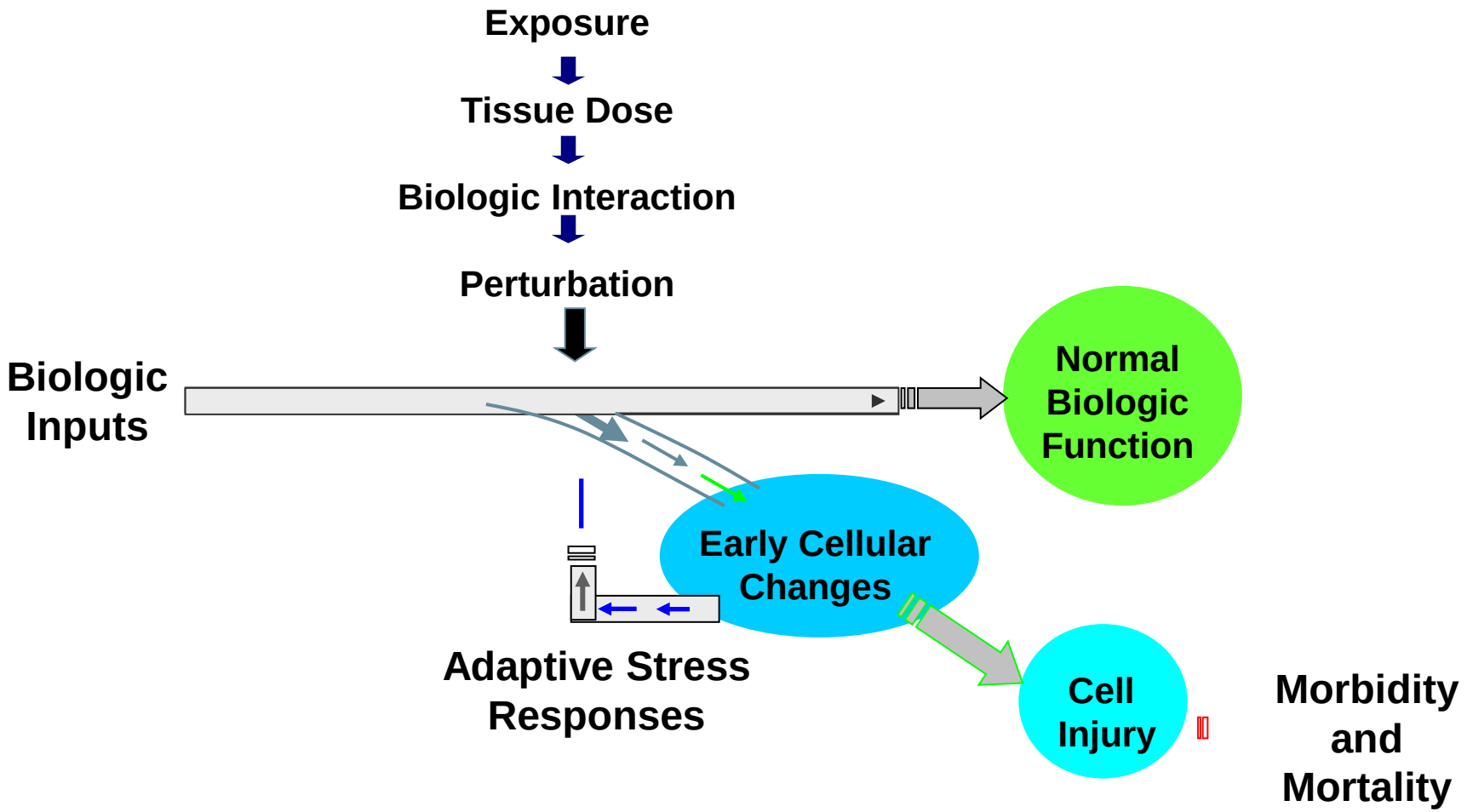
Mixtures Research
Division of the National Toxicology Program

- 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



NAS Report, 2007

Toxicity Testing in the 21st Century

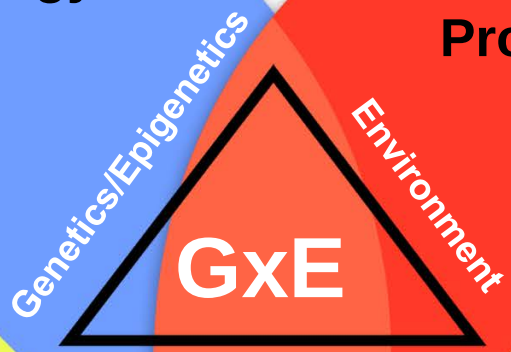
- Advancing Technology
  - In vitro screening
    - Human tissues more readily available
    - Increases in through-put
      - From 10's to 100,000 chemicals/year/assay
  - Omics
    - Genomics, Proteomics, Metabolomics
      - From single endpoints to high content data (10's of endpoints to 10,000's)
  - 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

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



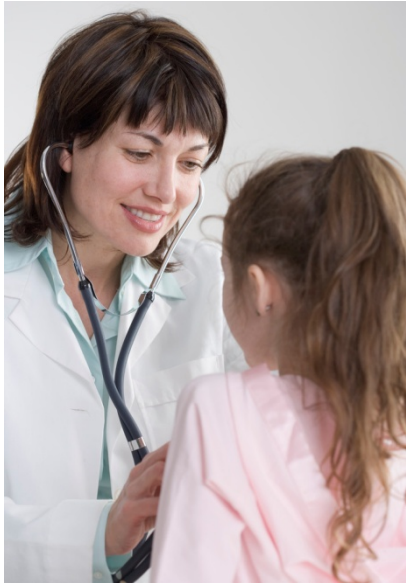
Human Genetics Program

Identify genetic variants

- GWA Studies
- Data Analysis
- Replication
- Sequencing

- Database
- Function
- Translation

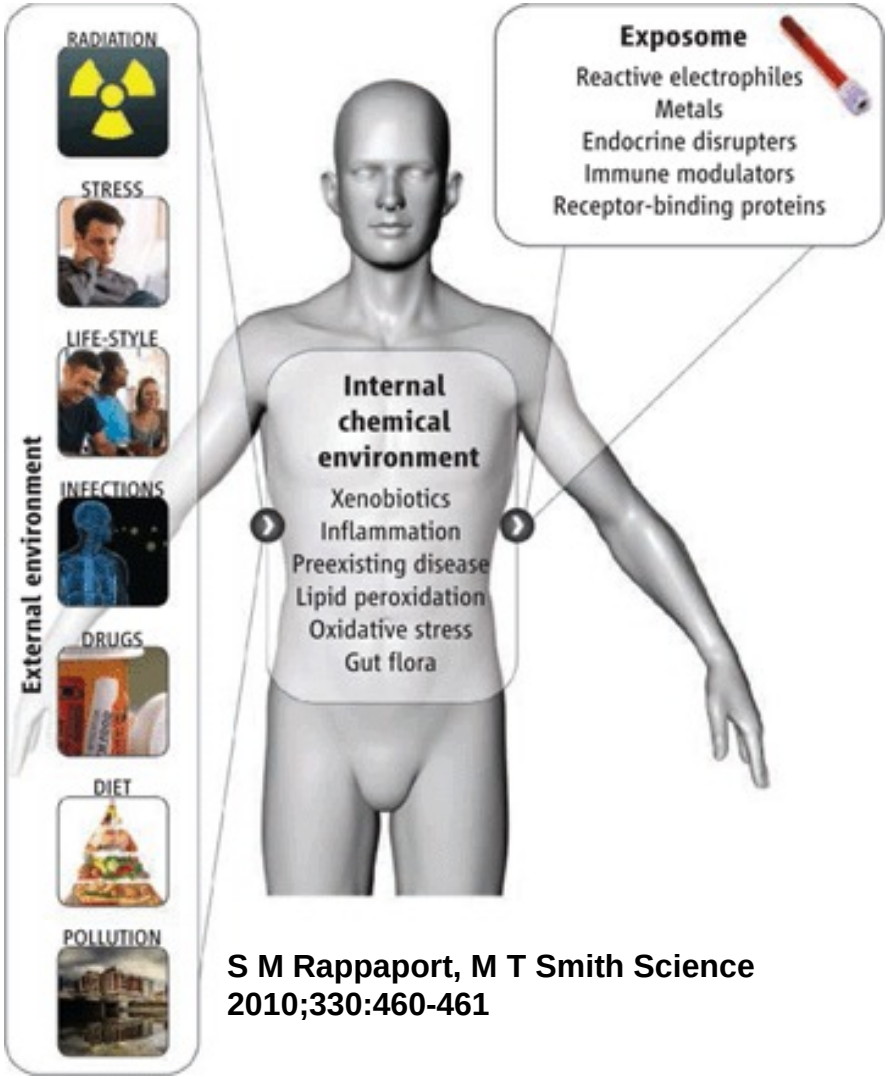
Exposure data



- 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

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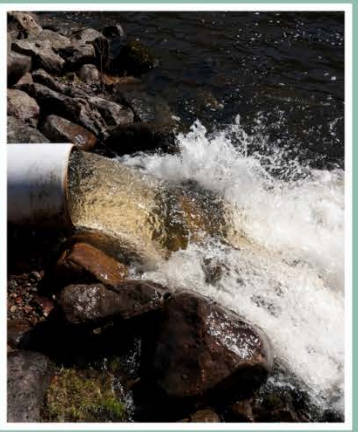

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