Eminent Toxicologist Lecture Series

Environmental Toxicology: Interconnections Between Human Health and Ecological Integrity

Society of Toxicology
Environmental Toxicology: Interconnections Between Human Health and Ecological Integrity

William H. Benson, PhD
Director, National Health and Environmental Effects Research Laboratory
Office of Research & Development, U.S. Environmental Protection Agency*

*This presentation does not represent EPA policy and mention of products or tradenames does not constitute a recommendation for use or endorsement.
Overview

- What Has Made a Career in Environmental Toxicology Rewarding
- Environmental and Scientific Challenges for the 21st Century
- Paradigm Shift in Regulatory Toxicology
  - Adverse Outcome Framework
- Interconnections Between Human Health and Ecological Integrity
  - SOT-SETAC Pellston Workshop Findings
- Concepts for Systems Thinking in Environmental Toxicology
What Has Made a Career in Environmental Toxicology Rewarding

• Fostering and working in a team environment
• Advancing the state of science and value of science
• Training and mentoring the next generation of science leaders
• Nurturing of a work environment that celebrates civility and joy of science
• Encouraging a social conscience – public service
• Conduct the right science, right – science for a purpose

Leading science is about leading people
Science for a Purpose

**PROBLEM**
Understand the problem facing society

**QUESTIONS**
Develop focused and insightful science questions raised by the problem

**APPROACHES**
Develop scientifically sound means to address the problem

**RESEARCH PRODUCTS**
High quality peer-reviewed models, methods, papers as products

**STRATEGIC PRODUCTS**
Integrated products that will be used to help solve problem

Do the right science for the right reason and make a difference
21st Century Challenges

- Climate adaptation and resilience
- Changing energy landscape
- Multi-pollutant exposure
- Increasing nitrogen and phosphorus levels impair water quality
- Susceptibility & environmental justice
- Thousands of new industrial chemicals and pesticides each year
- Chemical, biological, radiological-based terrorism
- Emerging materials, biotechnology, synthetic biology
Research to Address Scientific Challenges

• **Innovative** – foster creativity and stimulate transformational change
• **Integrative** – work collaboratively across disciplines
• **Systems thinking** – holistic approach to analysis on the way that a system’s constituent parts interrelate and how systems work over time and within the context of larger systems
• **Solution–oriented** – emphasis on developing sustainable solutions
• **Responsive** – provide relevant and timely results to inform environmental decision-making
• **Translational** – end users receive the necessary information to utilize research products to solve environmental problems
Only a tiny fraction of the compounds around us have been evaluated for risk

- Chemicals used by U.S. consumers and industry: >100,000
- Tested *in vivo*: <500

Water quality criteria/standards:

- Approximately 100 pollutants

The unknown is a consequence of the conventional approach employed for regulatory toxicity testing.
Conventional Approach to Generating Data for Chemical Risk Assessment

• Whole animal tests focused on apical responses (survival, growth, reproduction) at organism level
• Wide range of potentially adverse effects assessed without necessarily understanding how or why they occur

Advantages: Well-defined, easily understood endpoints; substantial history/experience; “gold” standard datasets for high priority chemicals; in vivo systems are integrative responses

Disadvantages: Resource- (money, animal) and time-intensive (esp. for chronic tests); impossible to test more than a few chemicals; reliance on apical responses limits extrapolation (chemical-chemical; species-species; lab-field)
A Paradigm Shift in Regulatory Toxicology
Predicting Chemical Toxicity with Limited Data

• Identify “normal” biological pathways whose perturbation results in adverse responses to chemicals
• Determine chemical characteristics that enable them to perturb these pathways
• Develop approaches to measure or predict these characteristics
  – *In silico* (computational) methods (e.g., QSAR, network models)
  – *In vitro* (e.g., HTP) toxicity pathway assays
  – *In vivo* tests with pathway-based endpoints (“biomarkers”)

Eminent Toxicologist Lecture Series • Society of Toxicology
Computational Approaches for Predictive Toxicology: QSARs

What is QSAR

- A QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics.
- QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these “rules” can be used to evaluate the activity of new compounds.

Fathead Minnow Acute Toxicity

96h Log LC50 (mg/L)

Log Kow

Eminent Toxicologist Lecture Series • Society of Toxicology
In Vitro Approaches to Predictive Toxicology: HTP Testing

Introduction

ToxCast

> 600 assays, >2000 chemicals

ToxCast HTS Assays

Biochemical Assays
- Protein families
  - GPCR
  - NR
  - Kinase
  - Phosphatase
  - Pro tease
  - Other enzyme
  - Ion channel
  - Transporter

Assay formats
- Radioligand binding
- Enzyme activity
- Co-activator recruitment

Cellular Assays
- Cell lines
  - HepG2 human hepatoblastoma
  - A549 human lung carcinoma
  - HEK 293 human embryonic kidney

- Primary cells
  - Human endothelial cells
  - Human monocytes
  - Human keratinocytes
  - Human fibroblasts
  - Human proximal tubule kidney cells
  - Human small airway epithelial cells
  - Rat hepatocytes
  - Mouse embryonic stem cells (Sid Hunter)

- Biotransformation competent cells
  - Primary rat hepatocytes
  - Primary human hepatocytes

- Assay formats
  - Cytotoxicity
  - Reporter gene
  - Gene expression
  - Biomarker production
  - High-content imaging for cellular phenotype

1536 well HTS
10,000 chemicals
25 assays per year

Eminent Toxicologist Lecture Series • Society of Toxicology
In Vivo Approaches to Predictive Toxicology

• In vivo exposures/tests help obviate uncertainties associated with computational/in vitro systems (e.g., metabolism, pharmacokinetics, integrative, pathway complexity, etc.)

• Evolving technologies in molecular biology/analytical chemistry (e.g., ‘omics) enable rapid measurement of large numbers of biological changes associated with short-term perturbations (hours-days)

• Concurrent advances in systems/network biology enable an increasingly coherent evaluation of this type of high content data, as well as more traditional biomarker information (e.g., PCR, ELISA, RIA, histology)
An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment.

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Macro-Molecular Interactions</th>
<th>Cellular Responses</th>
<th>Organ Responses</th>
<th>Organism Responses</th>
<th>Population Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Properties</td>
<td>Receptor/Ligand Interaction</td>
<td>Gene activation</td>
<td>Altered physiology</td>
<td>Lethality</td>
<td>Structure</td>
</tr>
<tr>
<td></td>
<td>DNA Binding</td>
<td>Protein production</td>
<td>Disrupted homeostasis</td>
<td>Impaired Development</td>
<td>Recruitment</td>
</tr>
<tr>
<td></td>
<td>Protein Oxidation</td>
<td>Altered signaling</td>
<td>Altered tissue development/function</td>
<td>Impaired Reproduction</td>
<td>Extinction</td>
</tr>
</tbody>
</table>

Novel Attributes of the AOP Framework

- Establishes common, unambiguous terminology as basis for communication among scientists and between scientists and risk assessors
- Promotes a chemical “agnostic” approach to understanding pathway perturbation, highlighting evaluation of chemicals based on biological similarity
- Provides a basis for establishment of causal linkages between molecular/biochemical endpoints and apical outcomes that can be assessed as to “fit for purpose” using WoE-based approaches*

How Does a Pathway-Based Approach Enhance Predictive Chemical Assessments?

- Provides basis for using alternative/mechanistic data to predict possible adverse effects
- Focuses/optimizes testing needed to assess risks
- Enhances cross-species extrapolation of chemical effects
- Supports assessment of effects of chemical mixtures

Receptor activation
Protein binding
DNA binding
Gene activation
Protein production
Altered signaling
Altered tissue
Disrupted homeostasis
Malformations
Organ dysfunction
Lethality

Eminent Toxicologist Lecture Series • Society of Toxicology
Regulatory Acceptance of the AOP Concept

Organisation for Economic Cooperation and Development
Extended Advisory Group on Molecular Screening and Toxicogenomics

WORKPLAN FOR DEVELOPMENT, ASSESSMENT, AND USE OF ADVERSE OUTCOME PATHWAYS (AOPs)

- Development of knowledge base for derivation and archiving of AOPs (AOP-KB)
- Publish formal guidance for AOP development, WoE assessment and implementation (2013/4)

http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm
SOT-SETAC Pellston Workshop–Interconnections Between Human Health and Ecological Integrity (June 2000)

- Policy Concepts and Applications
- Biological Bases for Similarities and Differences
- Characteristics and Implications of Interconnections
Conceptual Model

Di Giulio and Benson (2002)
The Natural System

Natural System Elements

<table>
<thead>
<tr>
<th>Physical Environment</th>
<th>Biota</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural resources</td>
<td>Human populations</td>
</tr>
<tr>
<td>Climate</td>
<td>Non-human populations</td>
</tr>
<tr>
<td>Environmental stressors</td>
<td>Population productivity</td>
</tr>
</tbody>
</table>

Eminent Toxicologist Lecture Series • Society of Toxicology
## Natural System Outputs

<table>
<thead>
<tr>
<th>Positive Flows</th>
<th>Negative Flows</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Materials</td>
<td>Pathogens</td>
</tr>
<tr>
<td>Energy resources</td>
<td>Climate extremes</td>
</tr>
<tr>
<td>Minerals</td>
<td>Natural disasters</td>
</tr>
<tr>
<td>Air</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
</tr>
<tr>
<td>Land</td>
<td></td>
</tr>
<tr>
<td>Soil</td>
<td></td>
</tr>
<tr>
<td>Forests</td>
<td></td>
</tr>
<tr>
<td>Environmental Amenities</td>
<td></td>
</tr>
<tr>
<td>Open space</td>
<td></td>
</tr>
<tr>
<td>Visibility</td>
<td></td>
</tr>
<tr>
<td>Natural Aesthetics</td>
<td></td>
</tr>
<tr>
<td>Recreational Opportunities</td>
<td></td>
</tr>
<tr>
<td>Materials Recycling</td>
<td></td>
</tr>
<tr>
<td>Habitat Maintenance</td>
<td></td>
</tr>
</tbody>
</table>

### Natural System Outputs

- Eminent Toxicologist Lecture Series
- Society of Toxicology
# The Social System

## Social System Elements

<table>
<thead>
<tr>
<th>Institutional</th>
<th>Cultural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic</td>
<td>Traditions/Customs</td>
</tr>
<tr>
<td>Political</td>
<td>Belief Systems</td>
</tr>
<tr>
<td>Legal</td>
<td>Values/Attitudes</td>
</tr>
<tr>
<td>Religious</td>
<td>Science/Knowledge Base</td>
</tr>
<tr>
<td>Educational</td>
<td>Technology</td>
</tr>
</tbody>
</table>

## Eminent Toxicologist Lecture Series • Society of Toxicology
Social System Outputs

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Stressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private goods and services</td>
<td>Pollution</td>
</tr>
<tr>
<td>Public goods and services</td>
<td>Waste</td>
</tr>
<tr>
<td>Technological innovations</td>
<td>Habitat destruction</td>
</tr>
<tr>
<td>New science/new knowledge</td>
<td>Urban sprawl</td>
</tr>
<tr>
<td>New philosophies/ethical standards</td>
<td>Overpopulation</td>
</tr>
<tr>
<td>Stability/justice/social harmony</td>
<td>Resource depletion</td>
</tr>
</tbody>
</table>
Well-Being

Defining Well-Being

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Well-Being</td>
</tr>
<tr>
<td>Social System Well-Being</td>
</tr>
<tr>
<td>Natural System Well-Being</td>
</tr>
<tr>
<td>Category</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Individual well-being</strong></td>
</tr>
<tr>
<td>Health</td>
</tr>
<tr>
<td>Wealth</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Social Justice</td>
</tr>
<tr>
<td>Psychological, Spiritual</td>
</tr>
<tr>
<td><strong>Social system well-being</strong></td>
</tr>
<tr>
<td>Sustainability</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Social Justice</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Peace and Stability</td>
</tr>
<tr>
<td><strong>Natural system well-being</strong></td>
</tr>
<tr>
<td>Health</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Wealth</td>
</tr>
<tr>
<td>Sustainability</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Conceptual Model

• Requirements for Implementation
  – Greater stakeholder involvement and use of decision science to encourage systems thinking about complex problems
  – Effective communication among scientists, policy-makers, and the public–acknowledge areas of uncertainty and be proactive
  – Reduce fragmentation of regulatory systems so that concerns for protection of human health are not segregated from concerns for protection of ecosystems–an integrated approach
  – Community involvement–use local knowledge while respecting the values, traditions and priorities of a community
Conservation Medicine, EcoHealth and One Health: Evolving Paradigms Building Transdisciplinary Collaborations, Integrative Research and Local Capacity

One Health is the collaborative effort of multiple disciples—Working locally, nationally, and globally—to attain optimal health for people, animals, plants, and our environment

A. Alonso Aguirre, Environmental Science and Policy, George Mason University, Fairfax, VA, USA  TP097
Conceptual Model

Di Giulio and Benson (2002)
Understanding Biological & Physical Systems Informs Decision Making

Need to utilize systems-based thinking and approaches at multiple scales to solve environmental challenges.
Computational Science

- Large Data Sets
- Alternative Models
- Species extrapolation

Experimental & Observational Science

- Knowledge gaps
- Novel applications
Thank you!
Key References

- American Veterinary Medical Association One Health Initiative Task Force. 2008. One Health: A New Professional Imperative. Schaumberg, IL, USA.