A More Efficient and Effective Testing and Assessment Paradigm for Chemical Risk Management

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Mission Statement –

- Best possible regulatory decisions to protect public health and environment.
- Rely on all best available scientific information.
- External Peer-Review; Public Participation.

Goal – Timely & targeted credible information to inform decisions.

Benefits:
- Resource Savings
- Efficiency
- Increase Reliability
- Public Trust
Challenges for Risk Assessment

- Risk Management Tools
- Risk Assessment Capability & Capacity
- Scientific & Technological Advancement
Common Risk Management Needs

Ecological & Human Health Risk Assessment

- Transparency & trust in decision-making.
- Resource demands: Effectiveness and efficiency.
- Spatial, temporal & biological decision scales.
- Integration of multiple stressors: Chemical and Non-Chemical.
The committee encourages EPA to focus greater attention on design in the formative stages of risk assessment, specifically on planning and scoping and problem formulation, as articulated in EPA guidance for ecologic and cumulative risk assessment (EPA 1998, 2003).
Ecological Risk Assessment

PROBLEM FORMULATION

Characterization of Exposure
Characterization of Ecological Effects

RISK CHARACTERIZATION

Communicating Results to the Risk Manager

Risk Management

As Necessary: Acquire Data, Iterate Process,

Planning (Risk Assessor/Risk Manager Dialogue)
PROBLEM FORMULATION

ANALYSIS

RISK CHARACTERIZATION

Integrate Available Information

- Source and Exposure Characteristics
- Ecosystem Potentially at Risk
- Ecological Effects

- Assessment Endpoints
- Conceptual Model
- Analysis Plan

Planning (Risk Assessor/Risk Manager Dialogue)

As Necessary: Acquire Data, Iterate Process, Monitor Results
Objective:
Foster transformative paradigm shift based largely on increased use of *in vitro* and *in silico* systems that will:

- Broaden coverage of chemicals, endpoints, life stages.
- Reduce cost and time of testing, increase efficiency and flexibility.
- Use fewer animals.
- Provide more robust data using mode of action and dosimetry information.
Enhanced Integrated Approaches to Testing and Assessment

Progressive, Tiered-Evaluation Approach: “Integrate, Formulate, Target”

Combine existing exposure and toxicity data including information from new technologies (in silico, \textit{in vitro} and \textit{–omics}) to:

- Formulate hypotheses about the toxicity potential of a chemical or a chemical category.
- Target further data needs specific to a chemical or members of a chemical category for a given exposure.
II. Adverse Outcome Pathways – definition and example

Paradigm Shift in Toxicology: Pathway–based assessment to predict adversity.

Modified From NRC 2007
Spatial, Temporal and Biological Scales

Integration of Scales: Source to Outcome

Source

Environmental Contaminant

Exposure

Molecular Initiating Event

Cellular Effects

Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

Source to Outcome Pathway
Watersheds with Drinking Water Intakes
**Adverse Outcome Pathway**

**Structure Activity Relationships**
- Chemicals
- Pharmaco - kinetics
- Molecular Target
- Cellular Response
- Tissue Organ

**In vitro studies**

**Monitoring**
- Individual
- Population

**In vivo studies**

**Toxicity Pathways**

**Key events or predictive relationships spanning levels of biological organization**
- Molecular initiating event
- Adverse outcome relevant to risk assessment

**Greater Toxicological Understanding**

**Greater Risk Relevance**
Examining scientific and technical issues related to methods and assumptions used by EPA, FWS, and NOAA to carry out joint responsibilities under the ESA and FIFRA.
NAS Review of Ecological Risk Assessments Under FIFRA and ESA

Charge Questions - Topic Areas:

- **Best Available Scientific Data & Information**
- **Geospatial Information and Datasets**
- **Mixtures**
- **Sub-lethal, Indirect, and Cumulative Effects**
- **Models**
- **Interpretation of Uncertainty**
Building Capacity for Explicit Risk Assessments

Habitat/Biota Distribution Data Layers
Habitat-Species Response
Population Models
Spatial Models
Chemical Data Layers
Chemical, Species Dose-Response Data & Models
Species Physiology Data
Demographic Data
Life History Data

OUTCOME: Efficient-effective site-specific risk assessment
Moving Forward – “Back to the Future”

The technology may be “new”, but the logic for advancing the science to change risk assessment and risk management is not.

OECD Principles for QSAR Validation: Transparency & Utility for a Specified Application

- Predicted endpoint is defined.
- Mechanistic interpretation associated with predictions, if possible.
- Defined chemical domain of applicability for the model.
- Appropriate measures of goodness of fit, robustness, ability to predict.
- An unambiguous algorithm.
Challenges to Accelerate Risk Assessment in the 21st Century

Overall objectives are monumental.
- Incremental steps; identify opportunities for success; focus on tangible applications (categories, read across, priority setting).

Building libraries of information will take time.
- Effective use of information technology can help accelerate AOP discovery, development, and evaluation.

Establishing linkages depicted in AOPs.
- Support transition from qualitative to quantitative uses; species and chemical extrapolations.

Establishing linkages across toxicology (human health and ecology).
- Multi-talented individuals and teams.

Continuum of learning and refining.