



A MORE EFFICIENT AND EFFECTIVE TESTING AND ASSESSMENT PARADIGM FOR CHEMICAL RISK MANAGEMENT:

A REGULATORY PROGRAM VIEW

SAB Briefing May 2012



Mission Statement

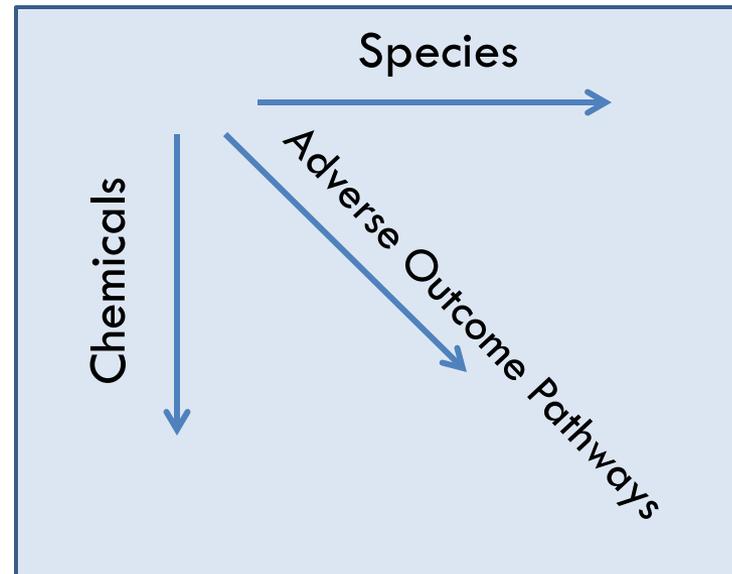
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- Sound regulatory decisions that are protective of public health and environment
- High quality, transparent risk assessments based on best available scientific information



Managing Chemical Risks

- Safety Evaluations Done for Human and Ecological Risks
 - ▣ Many chemicals
 - Data Availability/Quality Varies Extensively
 - ▣ Many possible adverse effects
 - ▣ Many species



Driver of Science



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Challenges: Managing Chemical Risks

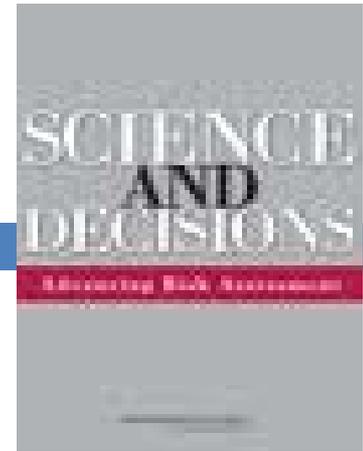


- Large number of chemicals to review with many possible adverse outcomes and many species to consider
- Finite resources and time
- Public expectations for scientific soundness, transparency, and timeliness

Timely & targeted credible information to inform chemical risk management decisions

Problem Formulation

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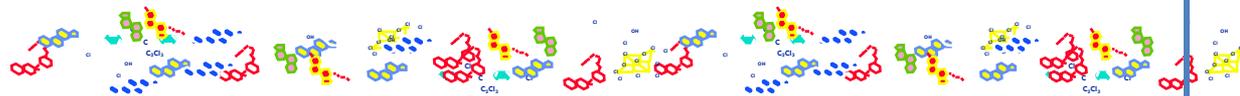


□ 2009 NRC Science & Decisions

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).

Problem Formulation

Chemical
Inventories



Existing
information

Information Needs
& Level of Complexity

Exposure
Information

Hazard Information
In vivo, in vitro, (Q)SAR, Read
Across

Targeted data
collection

Risk Assessment & Risk
Management

TIERED

Computation Toxicology



“Back to the Future”

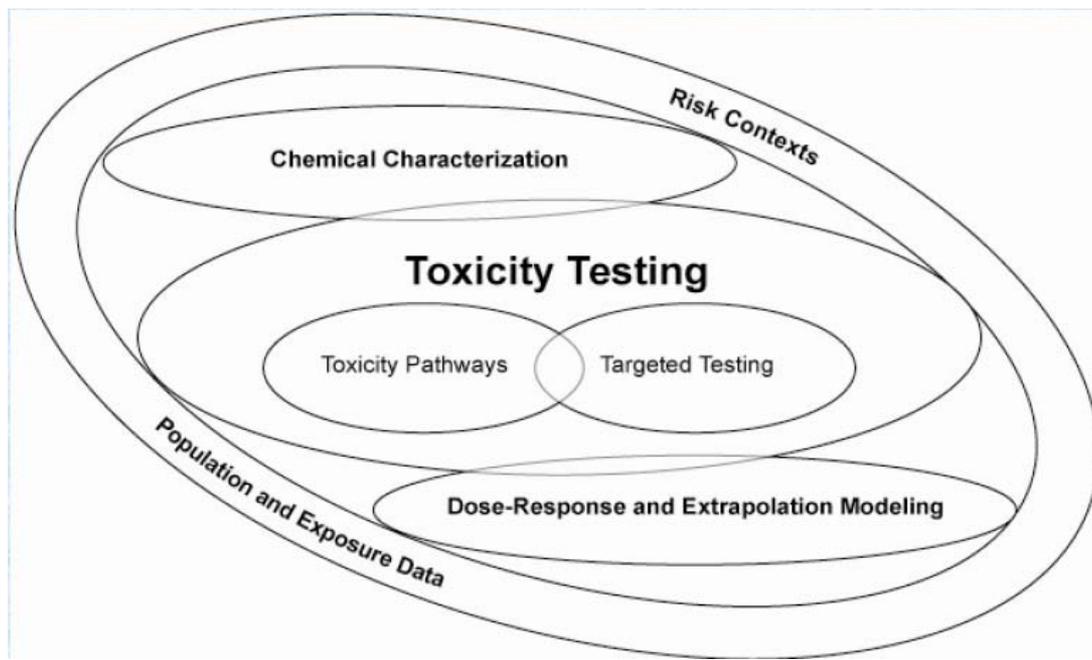
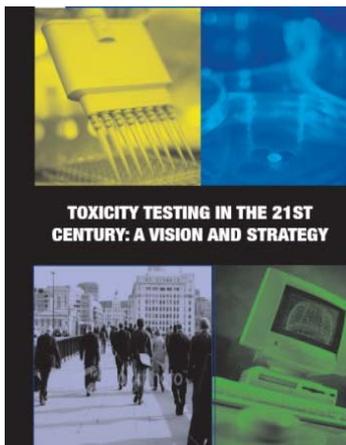
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- (Q)SAR –Generally used as part of an overall weight of the evidence in both ecological and human health risk assessments
 - Ecological risk – e.g., ASTER and ECOSAR are used to estimate toxicity to fish, invertebrates, and algae
 - Human health – e.g., oncologic, analogs and chemical categories are used to estimate hazards and target follow-up testing
- Mode of Action Analyses
 - e.g., previous SAB reviews, organic arsenic, chloroform

2007 NRC Toxicity Testing in the 21st Century



- Recognized technological advances
- Integrated and targeted test strategies
 - ▣ Use knowledge of adverse outcome pathways
 - ▣ Increased use of *in vitro* and *in silico* systems



Spatial, Temporal and Biological Scales

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Integration of Scales: Source to Outcome



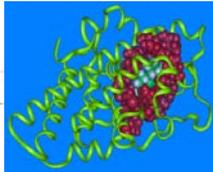
Source



Environmental Contaminant



Exposure



Molecular Initiating Event



Cellular Effects



Individual



Population

Community



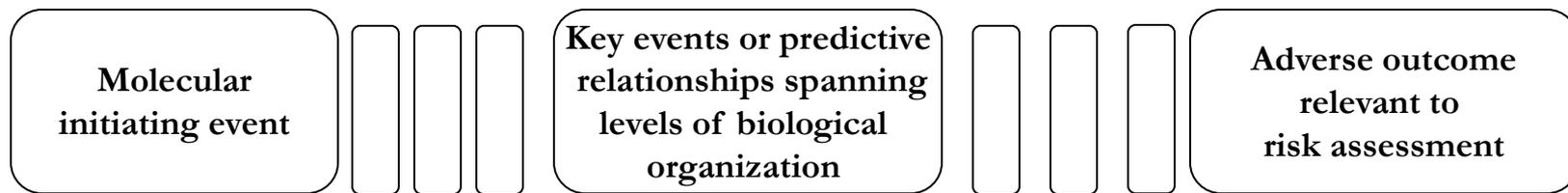
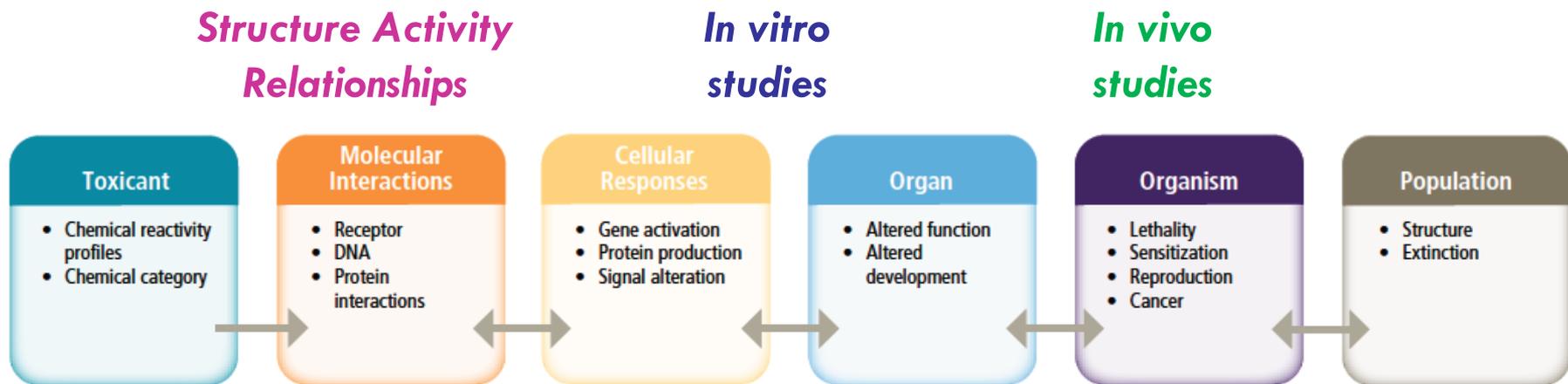
Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

Source to Outcome Pathway

ADVERSE OUTCOME PATHWAY



Greater Toxicological Understanding
(Qualitative AOP)



Greater Risk Relevance
(Quantitative AOP)

Adverse Outcome Pathway (AOP)



- Conceptual basis for:
 - ▣ Developing and applying lower tiered tests & non-animal models (e.g., QSAR, *in vitro*, HTS)
 - ▣ Forming Chemical Categories & Read Across methods
 - ▣ Better dosimetrics and biomarkers for experimental studies, epidemiology, population monitoring and surveillance
 - ▣ Species extrapolation



Regulatory Safety Assessment

- Meeting Common Needs - A more predictive (relevant), reliable, faster, less expensive testing & assessment paradigm that enables focus.

Move from Empirical to Mechanistic

(Toxicity evaluations should be hypothesis generating & testing rather than one size fits all)

Enhanced Integrated Approaches to Testing and Assessment



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

- Combine existing exposure and toxicity data including information from new technologies (in silico, in vitro, 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.

Adverse Outcome Pathway Concept
Means of Strengthening

Chemical Risk Management: Transitioning “New Technologies”



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- Depends on how much uncertainty is accepted in the exposure and decision context
- Initial transition – Qualitative
 - ▣ Under what conditions of exposure would testing need to be minimally investigated (targeted)
 - Strengthen priority setting/screening for data-limited chemicals to focus on in vivo testing
- Transition away from chemical-by-chemical approaches
 - ▣ formation of chemical categories with shared biological and structured properties for read across

Continuum of Learning & Refining

Decision (Regulatory) Context

Data-Limited
Situations

Comprehensive
Data

Priority Setting

Quantitative Risk
Assessment



Lower

Level of Confidence
(Uncertainties Acceptable?)

Higher

Ground Truthing to Apical Toxicity

Qualitative



Quantitative

Adverse Outcome Pathway

Expert Peer Review - May 2011 FIFRA Scientific Advisory Panel



- Expressed favor for use of AOP methodology to support vision for employing IATA strategies
 - ▣ sensible and logical way to make risk assessment process more efficient & informative.

- Process of continued learning will lend itself to broader stakeholder input and transparency as the process develops, refines and matures.

- Research will involve *in vivo* studies in parallel with *in vitro* methods

International Partnerships



For example,

- OECD Adverse Outcome Project
- OECD Metabolism Database and Predictive Systems (MetaPath) Project
- NAFTA QSAR Guidance
- WHO Mode of Action Umbrella Project

Organization for Economic Cooperation & Development (OECD)
North American Free Trade Agreement (NAFTA)
WHO International Program for Chemical Safety, etc



Stakeholder Engagement

- Transparency and public participation is necessary
- Public trust that approach is as good or better than current

Stakeholder support is critical
to moving forward

- Federal Advisory Committee--Pesticide Program Dialogue Committee (PPDC) 21st Century Toxicology/New Integrated Testing Strategies Workgroup

<http://epa.gov/pesticides/ppdc/testing/index.html>

Challenges to Accelerate Toxicity Testing in the 21st Century



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- Overall objectives are monumental (SAP)
 - ▣ But there will be incremental steps
- Building Libraries of AOPs will take time
 - ▣ But effective use of 'omics' and HTS approaches can help accelerate AOP discovery, development, and evaluation
- Establishing linkages depicted in AOPs
 - ▣ support transition from qualitative use of AOPs to quantitative uses (dose response relationships)
- Understanding species differences in AOPs
 - ▣ ecological risk assessment

Successful Transition of 21st Century Methods into Regulatory Practice



- Begin with the end in mind (Problem Formulation)
- Build transparent strategy with sound scientific basis around risk management needs
 - ▣ Research in concert with regulatory dialogue
 - ▣ Incremental application to decision making
 - ▣ New methods flow from expert peer review and transparency
- Identify partners
- Ensure support of your stakeholders





“Back to the Future”

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Scientific Transparency, Structure & Rigor

- **OECD Principles for QSAR Validation**

- 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.

- **WHO IPCS Framework for Mode of Action Analysis**

- Criteria to evaluate evidence
 - Biological plausibility, consistency, coherence, dose response and temporal concordance