Tools for Predicting the Toxicity of Chemicals to Aquatic Animal Species

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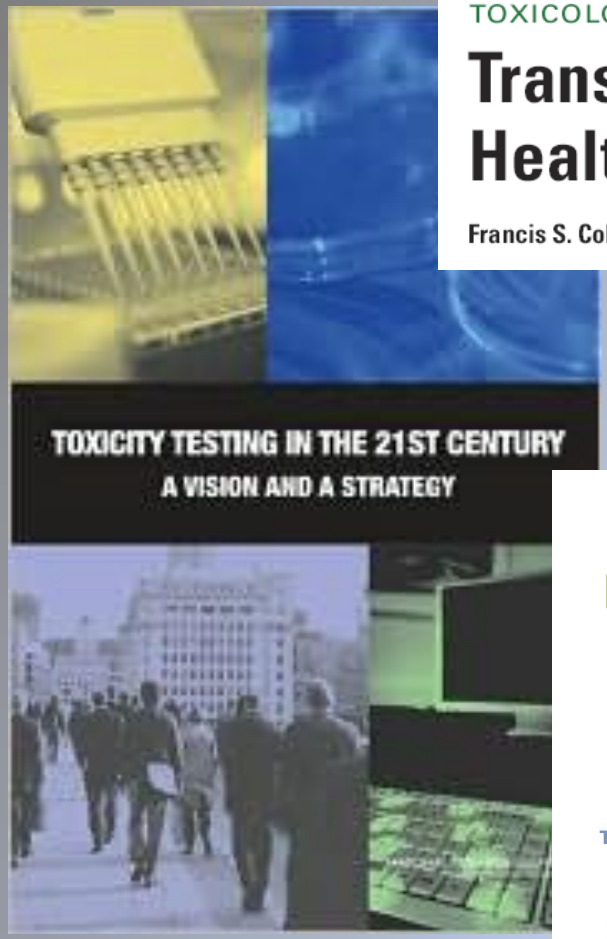
Stakeholder meeting, Washington DC, December 1, 2010

Wade Lehmann, presenter



POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

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Meeting *the* Scientific Needs *of* Ecological RISK Assessment *in* a Regulatory Context

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Three strategies could move both science and regulation forward.

During the past decade, the field of ecological risk assessment has progressed considerably. Advances have come from such international bodies as

Increasing efficiency, cost-effectiveness, and focus

Risk assessment is a tiered process distinguished by levels of increasing complexity, beginning with the preliminary

Intelligent Testing Strategies in Ecotoxicology: Mode of Action Approach for Specifically Acting Chemicals

Technical Report No. 102

[illegible]
Brussels, December 2007

Purpose Statement

Present an overview of predictive tools that may be useful to U.S. Environmental Protection Agency (USEPA) risk assessors along with States, Regional and Tribal risk assessors in estimating data to address a level of adverse effect (toxicity) of pesticide active ingredients and degradates to aquatic animals.

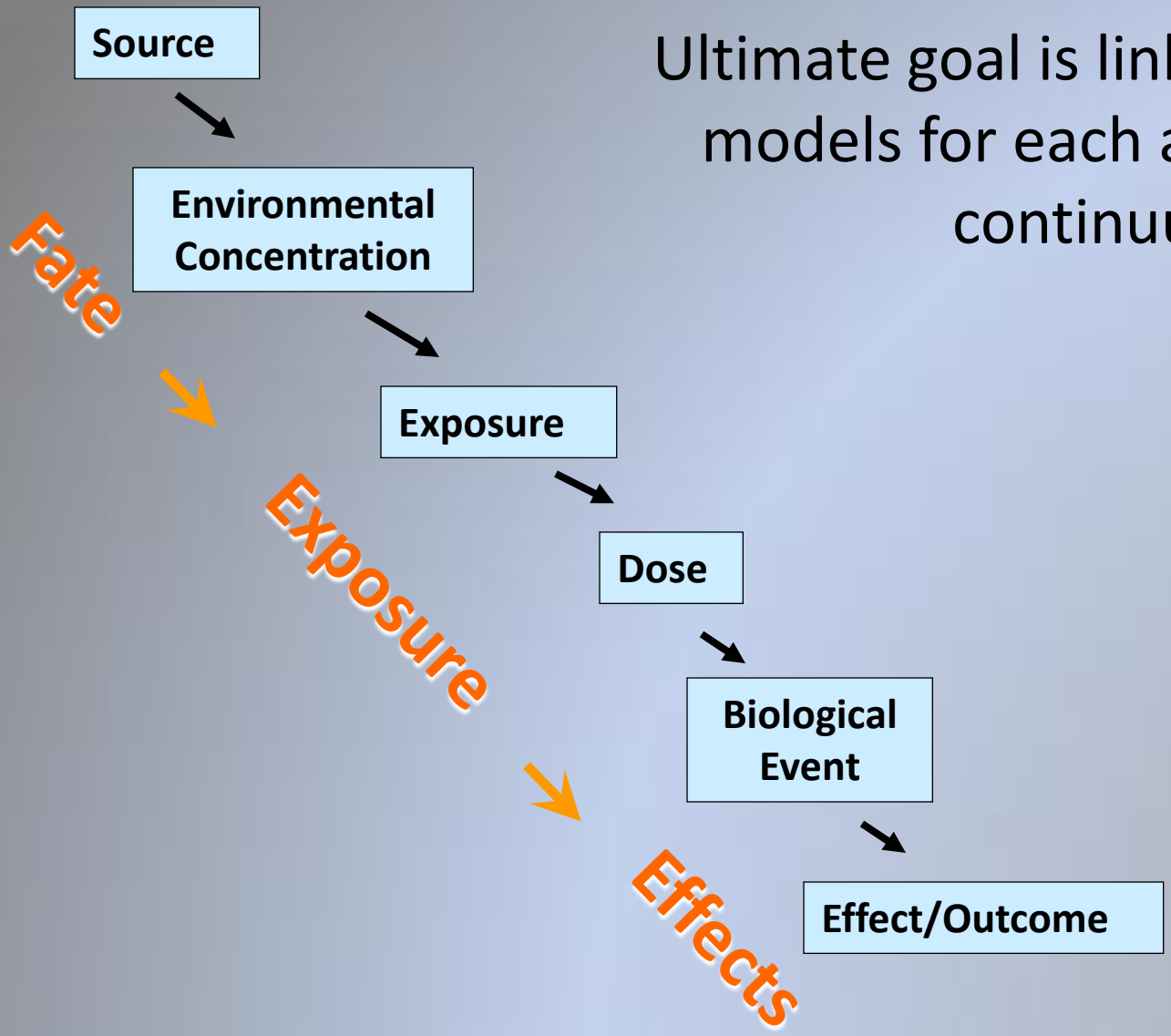
What is Predictive Toxicology?

An in-depth survey of strategies to characterize chemical structures and biological systems-covering prediction methods and algorithms, sources of high-quality toxicity data, the most important commercial and noncommercial predictive toxicology programs, and advanced technologies in computational chemistry and biology, statistics, and data mining.

Predictive Toxicology The Book, CRC Press, 2005

Role of Tools for Predicting Species Sensitivity

- Key Role – potential to reduce uncertainty
- Reduce reliance on “safety factors”
- Ability to derive estimated data
- Rationale for inclusion or exclusion of minimum acceptable data requirements (OW)
- Rationale for determining whether or not degradates of a chemical should be of toxicologic concern (OPP)



Ultimate goal is linked, predictive models for each aspect of the continuum.

Considerations

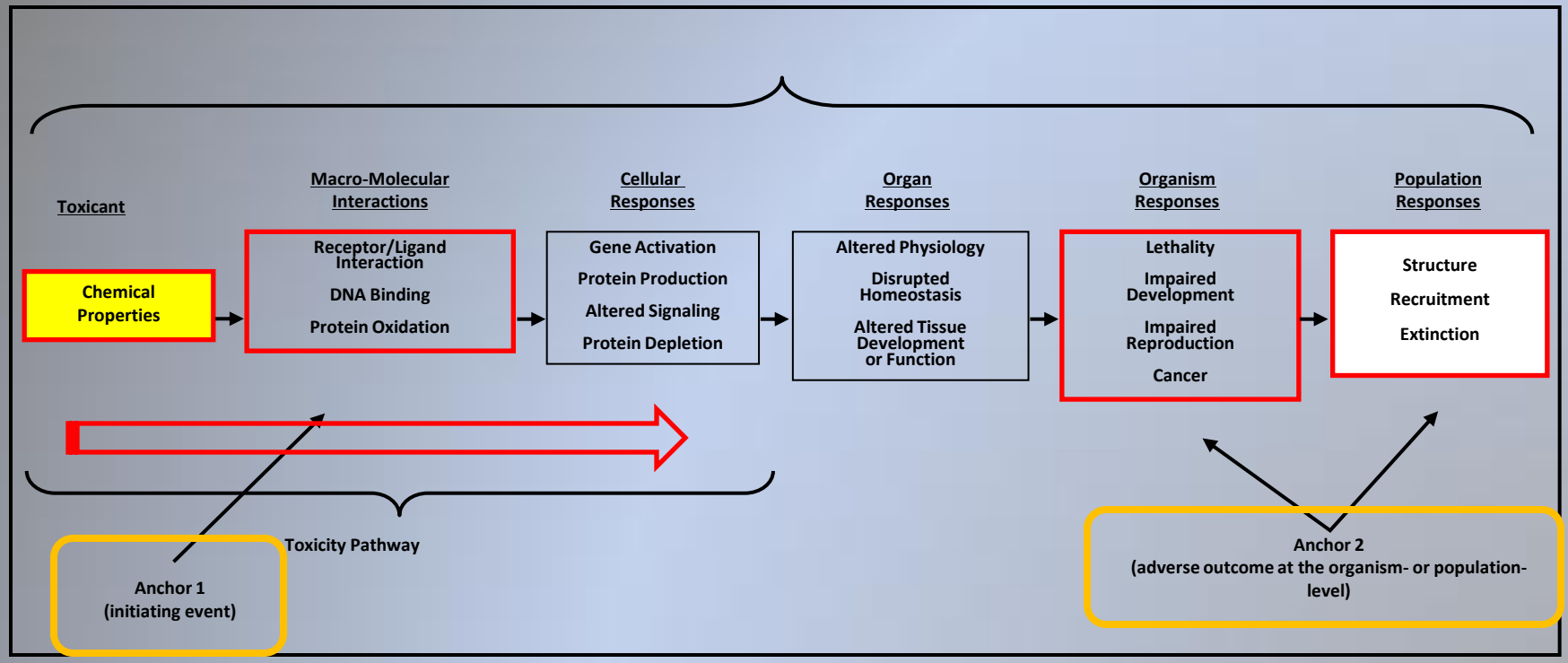
Mode of Action (MOA)

An understanding of selected key events and/or processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in a disease state or other adverse effect.

National Research Council report "Toxicity Testing in the 21st Century"

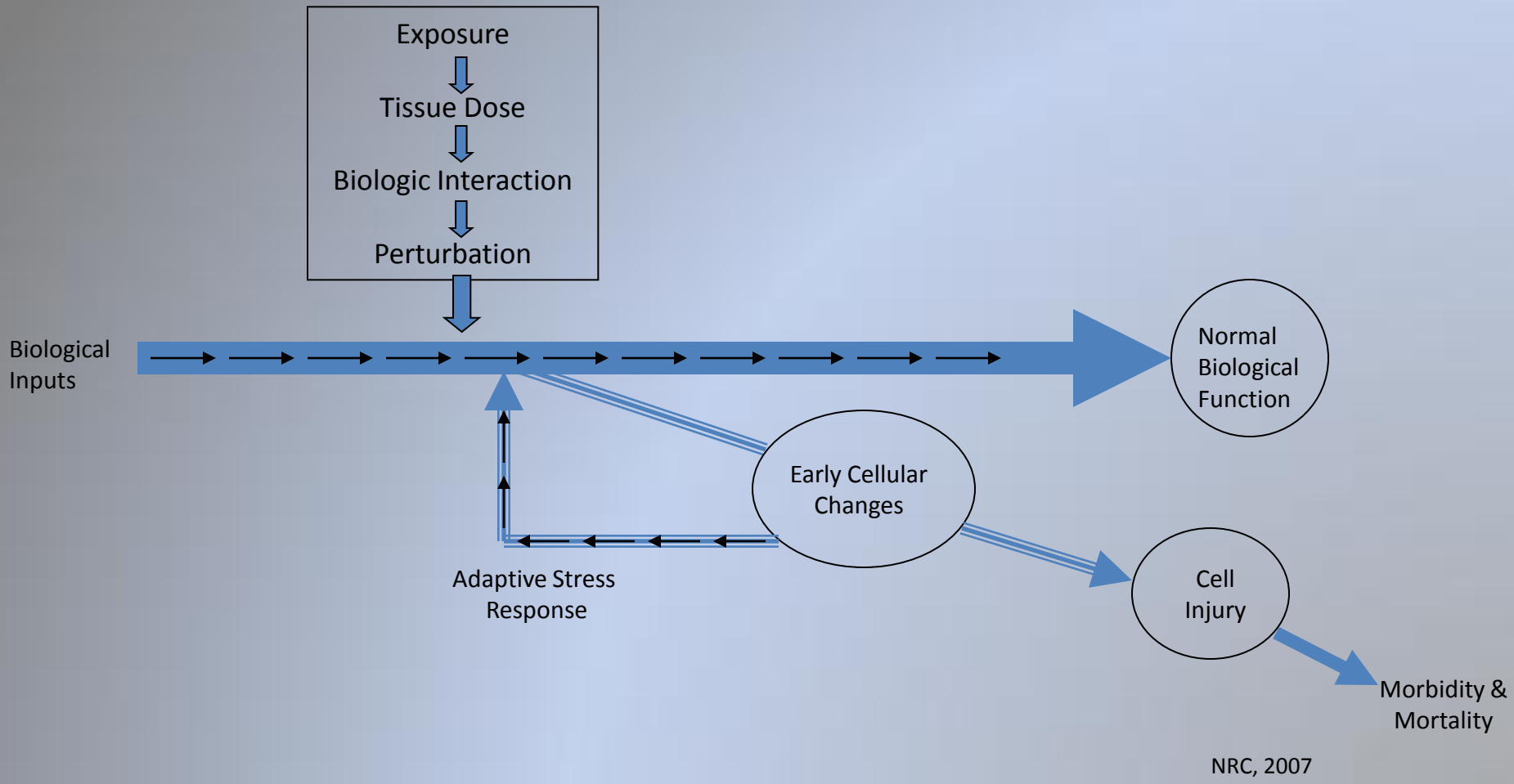
Considerations

Adverse Outcome Pathway (AOP)



modified from Ankley et al., 2010

Toxic Effect Pathway



NRC, 2007

Usage of Tools

- Current Data Requirements
- Predictive Tool Identification and Usage

Current Data Requirements

OPP Data Requirements

OW Data Requirements

SALMONID

SECOND FISH FAMILY

PLANKTONIC CRUSTACEAN

BENTHIC CRUSTACEAN

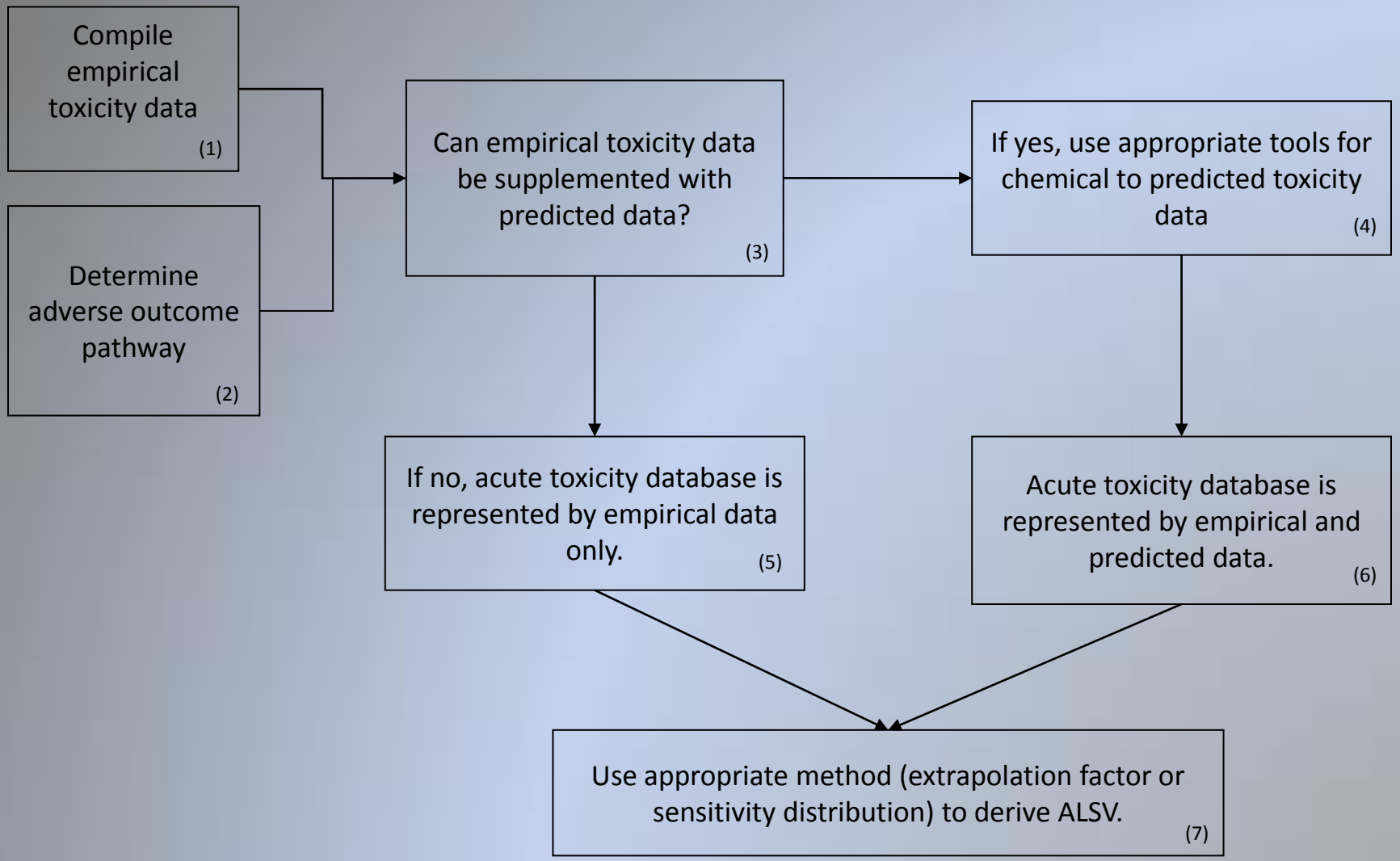
INSECT

OTHER INSECT OR MOLLUSCA

ROTIFERA, ANNELIDA, MOLLUSCA

CHORDATA

Proposed Method



Considerations in Approach

- These methods are one element in a multiple lines of evidence approach.
- Output should be weighted (qualitative vs quantitative) according to reliability and risk assessment context
- Has the approach followed the appropriate validation principles?
- How consistent is the prediction based on what is known about the chemical being evaluated?
- Identify uncertainties associated with the prediction
- What are the limitations of the selected models?

Predictive Tools

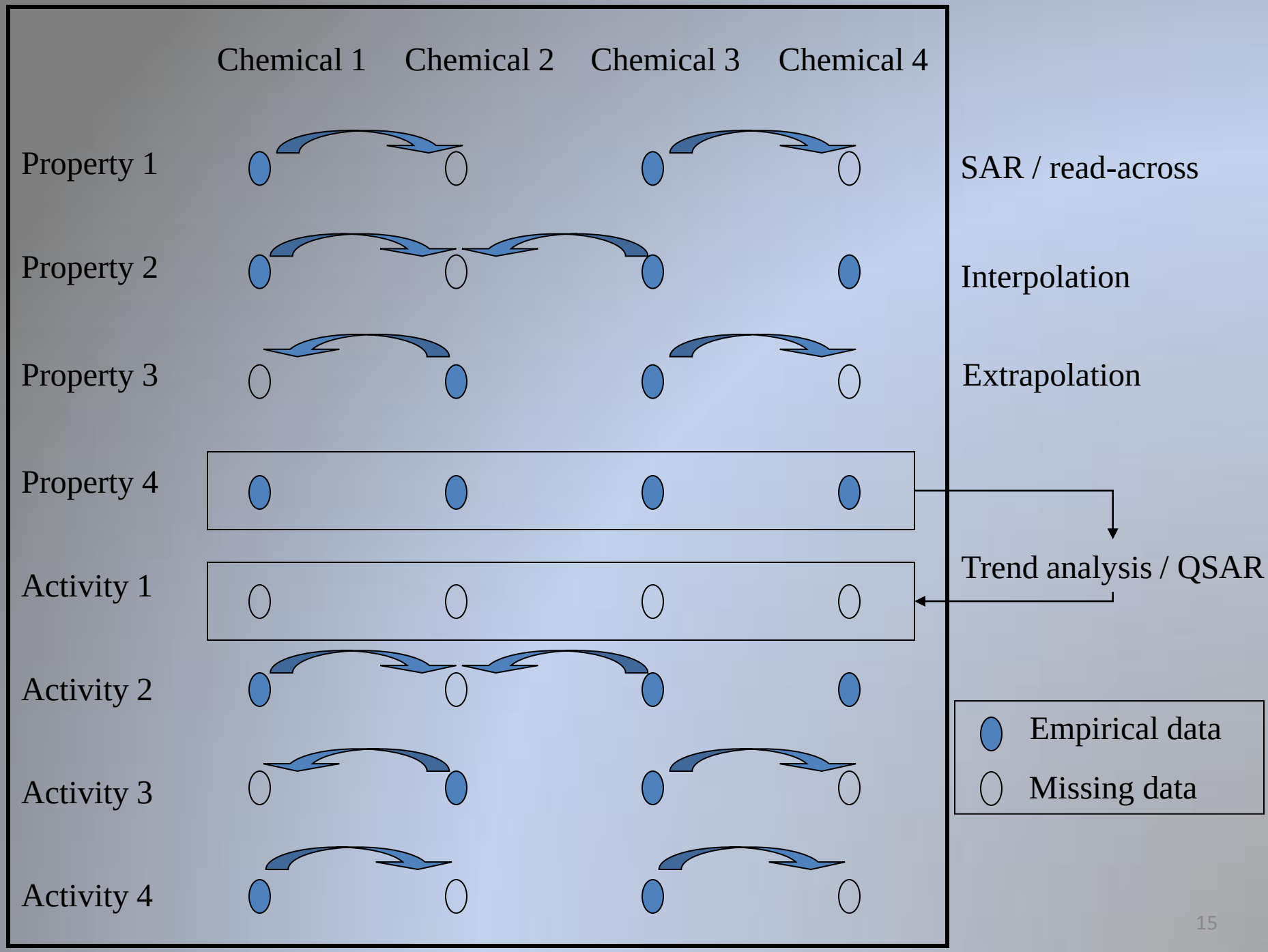
[Quantitative] Structure Activity Relationships

Read-Across/Bridging

webICE (Interspecies Correlation Estimates)

TCE (Time-Concentration Effect) models

ACRs


Chemical 1
Chemical 2
Chemical 3
Chemical 4
Property 1
Property 2
Property 3
Property 4
Activity 1
Activity 2
Activity 3
Activity 4
SAR / read-across
Interpolation
Extrapolation
Trend analysis / QSAR
Empirical data
Missing data

Predictive Tools

Read-Across / Bridging

Endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be “similar”.

Read-across process involves:

The identification of a chemical substructure or MOA that is common to two substances (analogues); and

The assumption that toxicological effects of each analogous substance in the set will show common behavior in relation to AOP (*i. e*., organophosphate pesticides)

Predictive Tools

Read-Across / Bridging

Parameter	ALLETHRIN	DIMETHRIN	DELTAMETHRIN	RESMETHRIN	PERMETHRIN	BIFENTHRIN
Fathead minnow LC50 values (ug/L)	53.0	62.0	??	6.16	16.0	??
Log P	5.52	6.57	7.02	7.11	7.61	8.15

Predictive Tools

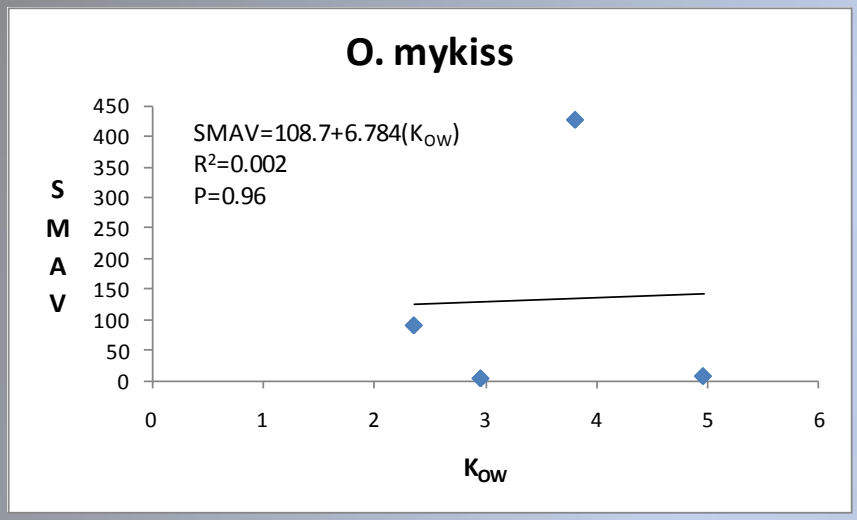
Read-Across / Bridging

Parameter	ALLETHRIN	DIMETHRIN	DELTAMETHRIN	RESMETHRIN	PERMETHRIN	BIFENTHRIN
Fathead minnow LC50 values (ug/L)	53.0	62.0	**27**	6.16	16.0	**7.9**
Log P	5.52	6.57	7.02	7.11	7.61	8.15

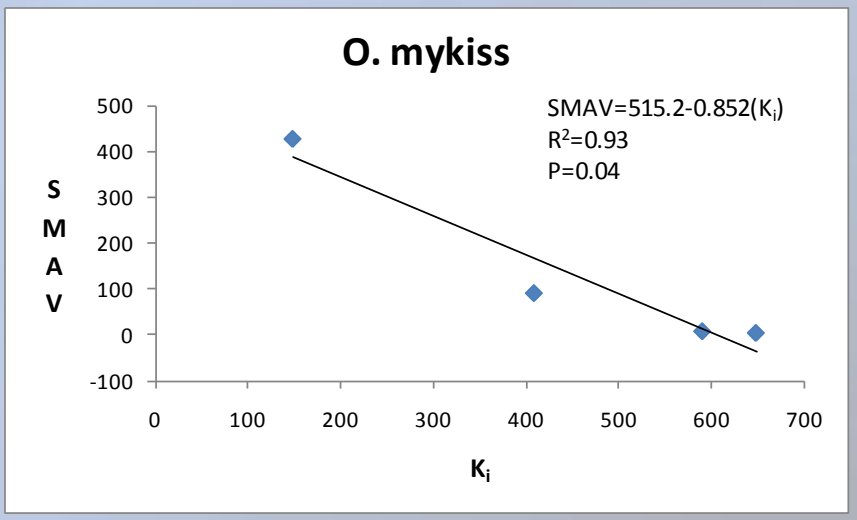
Predictive Tools

Read-Across / Bridging

Rainbow trout toxicity shows no relationship to K_{OW}.



Rainbow trout toxicity increases significantly (decreasing LC50) with increasing K_i.



Predictive Tools

[Quantitative] Structure Activity Relationships

Chemical structure is [quantitatively] correlated with a well defined action, *e.g.*, biological activity or chemical reactivity.

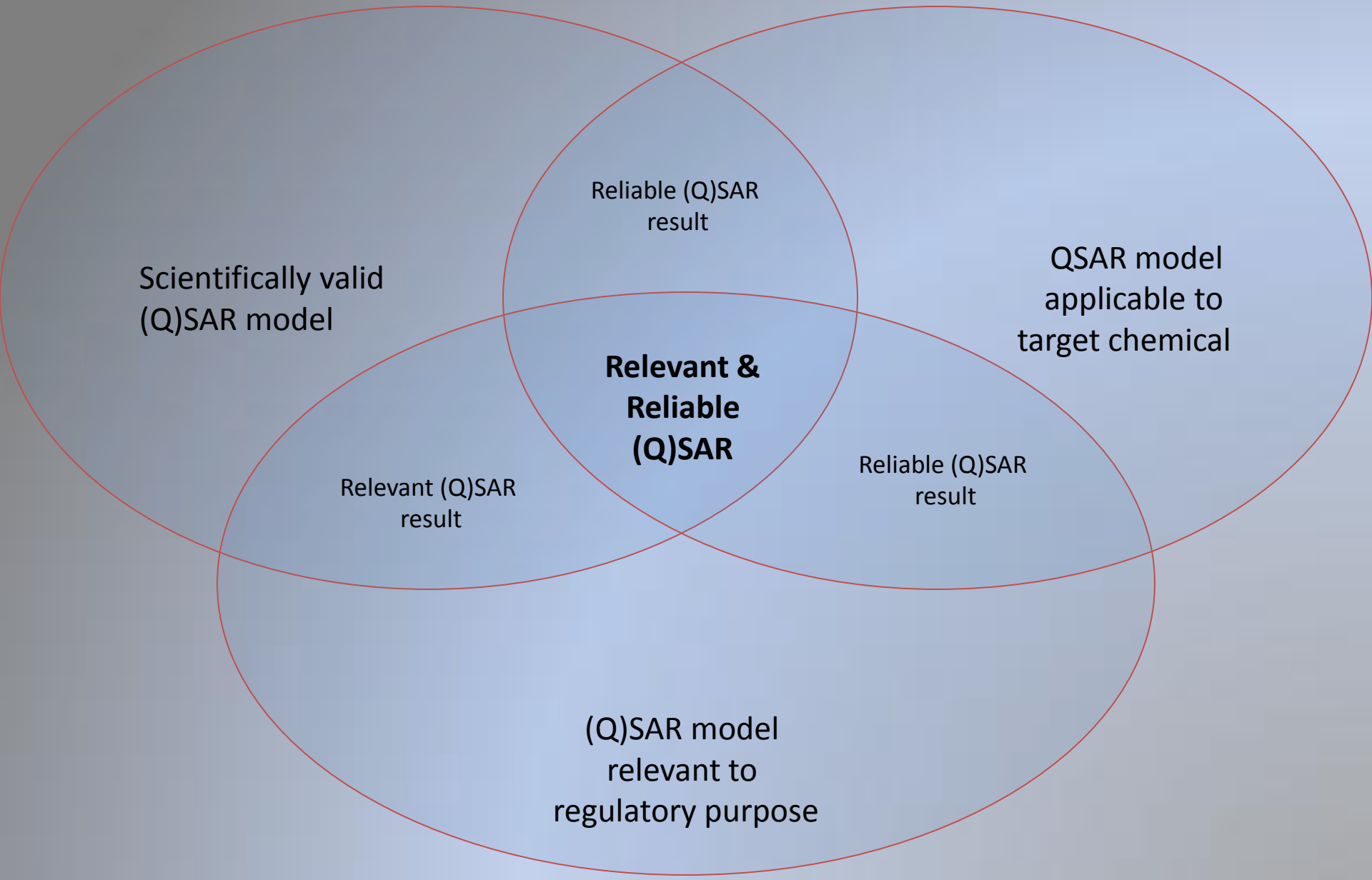
Example: EPA ECOSAR (Ecological Structure Activity Relationships)

Assumptions

Predictive Tools

OECD Principles for QSAR Validation

- A defined endpoint
- An unambiguous algorithm
- A defined domain of applicability
- Appropriate measures of goodness-of-fit, robustness, and predictive capacity.
- A mechanistic interpretation



Modified from ECHA 2010

Predictive Tools

Interspecies Correlation Estimation

Web-based tool that estimates acute toxicity (LC_{50} or EC_{50}) for a species, genus or family from a surrogate species.

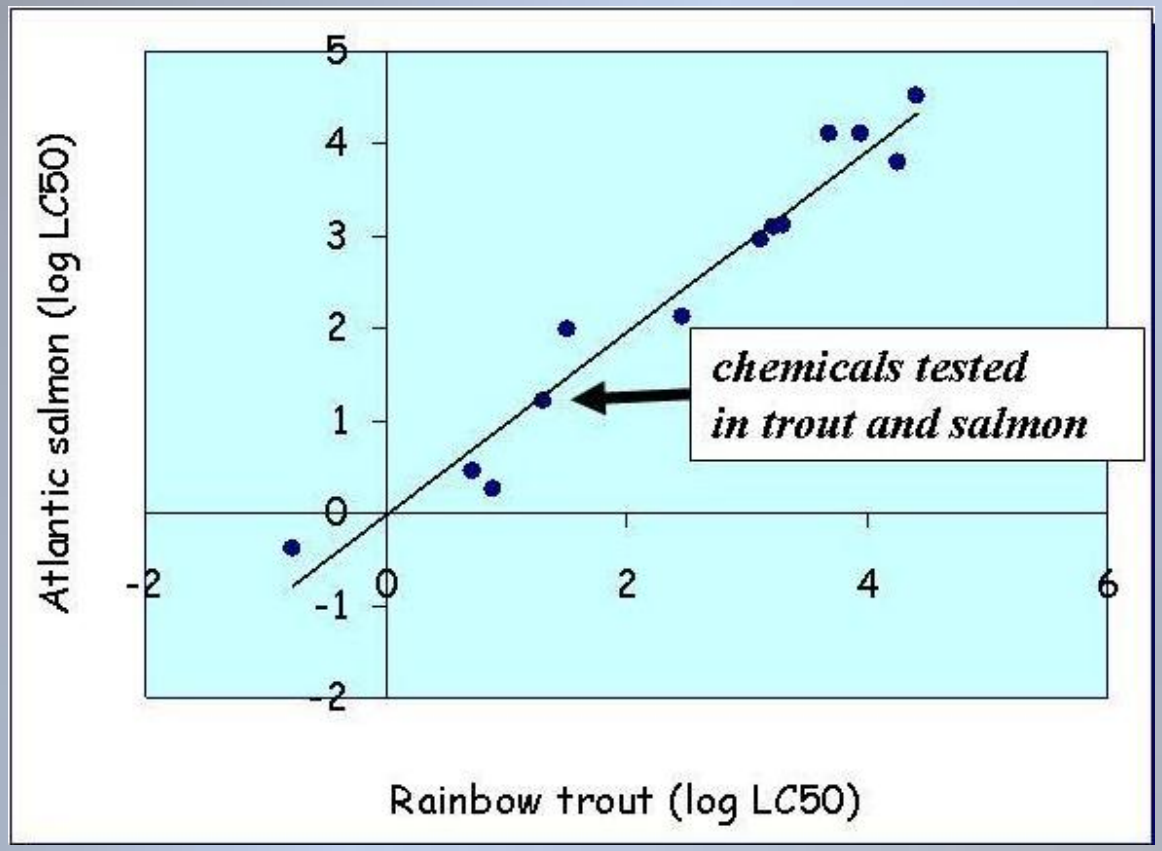
Uses of web-ICE in ecological effects assessment:

- Populates toxicity database;
- Allows for species sensitivity comparisons ;
- Taxa sensitivity estimation for endangered species;
- Quantifiable model confidence

Predictive Tools

Interspecies Correlation Estimation

ICE Models are Log-linear models of the relationship between the acute toxicity (eg. LC_{50}) of chemicals tested in two species.



Predictive Tools

Time-Concentration Effects Models (TCE)

- Use time-course to mortality data from acute toxicity tests to extrapolate to a prediction of chronic lethality
- Several different types
- Validated to predict chronic mortality

Predictive Tools

Acute-Chronic Ratios (ACR)

Used to estimate chronic toxicity in aquatic organisms for which acute toxicity is known, but chronic data are limited or absent

ACR = ratio of acute effect to chronic measure

eg. ACR= LC_{50} (or EC_{50}) ÷ NOEC (or MATC)

Predictive Tools

Acute-Chronic Ratios (ACR)

OPP use of ACRs

OW use of ACRs

Similarities in approaches by both OPP and OW:

Use of same assessment endpoints (survival, growth, and reproduction);

Control performance;

Dilution water quality and potential impacts on toxicity; and

Chronic data based on similar exposure duration and type of exposure.

Interpretation Framework For Predictive Tools

- Using OECD validation principles as a framework for guidance ([Q]SAR and beyond)
  - Defined endpoint
  - An unambiguous algorithm
  - Defined domain of applicability
  - Appropriate measures of goodness of fit, robustness, and predictive capacity
  - Mechanistic interpretation if possible
- Using guidance provided by tool developers
  - Defined criteria: Positive vs negative vs inconclusive associations and/or correlations
- Strengths and weaknesses of existing data estimation techniques for pesticide active ingredients

Considerations for Use of Predictive Tools

- Only one element in a multiple lines-of-evidence approach
  - Considered according to reliability, data availability/reliability for tool interpretation, and assessment context
- Ideally will have multiple predictions from multiple tools
  - Evaluate strengths and limitations of concordance approach
    - Reliability
    - Predictive performance
    - Domain of applicability

Considerations for Use of Predictive Tools (cont'd)

- Obtain predictions for test compound and similar (chemical category or class/MOA) data rich compounds, parent compound, and possibly metabolites

- Documentation of predictions and interpretations
  - Dependent on assessment context:
    - Screening – limited documentation
    - Criteria development – comprehensive documentation

Considerations for Use of Predictive Tools (cont'd)

Weight of Evidence and use of Best Professional Judgment

- Output from these predictive methods should be weighted (qualitative/quantitative) according to reliability, availability of specific data types (*e.g.*, *in vivo* study results), and assessment context (*e.g.*, identification of data requirements vs. hazard assessment decision).
- Keeping in mind the OECD Validation Principles for use of QSARs, and the Bradford Hill criteria for identification of AOPs, users should recognize that these are prediction methods and they have associated limitations.
- There are uncertainties regarding the variability and relevancy of predicted values. Many model estimates should only be considered when actual measured chemical-specific data are not available. Uncertainties should be noted.

Summary

Through this White Paper, the Agency (OW, OPP, ORD) presents an overview of predictive tools that may be useful in generating data for use in effects assessment and derivation of aquatic life screening values.

Each component of this approach should be evaluated, documented, and appropriately applied to a lines of evidence approach to estimating comparative taxonomic sensitivity to derived surrogate data values.