Development & Evaluation of Ecotoxicity Predictive Tools

EPA Development Team

Regional Stakeholder Meetings
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Outline

- Purpose and Scope
- Tools
- Application of Tools
- Interpretation of Predictions
- Other Considerations

Purpose and Scope

- **Present an overview of 21st century tools for EPA to use in generating estimated toxicity data for pesticides**
- **Tools will be used by both OW and OPP when:**
  - Acceptable chemical-specific data are not available in the open literature
  - Data requirements are not met according to the 1985 Guidelines or FIFRA Subdivision G, Parts 158.630 and 158.660; and/or
  - Additional data are required to reduce uncertainties in OPP assessments
- **Tools include, but not limited to:**
  - Quantitative/Qualitative Structure-Activity Relationships ([Q]SAR)
  - Read-across / data bridging
  - OECD / EPA chemical categories and/or mode of action inference
  - Acute-to-chronic ratios (ACR)
  - Interspecies correlation models (ICE)

Role of Tools for Predicting Species Sensitivity – How do they fit in?

- **Key Role – potential to reduce uncertainty**
- **Reduce reliance on "safety factors"**
  - Frequency of use
  - Magnitude of "safety" factor
- **Ability to derive estimated data**
- **May provide rationale for inclusion or exclusion of minimum acceptable data requirements**
  - Based on pesticide class/category
  - Based on mode of action
  - Based on taxonomic sensitivity

[Quantitative] Structure Activity Relationship ([Q]SAR)

- **Chemical structure is [quantitatively] correlated with a well defined action, *e.g.*, biological activity or chemical reactivity.**
- **Assumptions:**
  - Chemical's structure imparts properties that relate to biological activity
  - Chemicals that produce the same biological activity (toxicity; adverse effect) have something similar about their structure
  - Goal is to quantify 'structural similarity' imparting activity
- **Example: EPA ECOSAR (Ecological Structure Activity Relationships)**
  - ECOSAR is a library of [Q]SARs for predicting aquatic toxicity based on chemical structure
  - ECOSAR expert system for selecting the appropriate QSAR value
  - (http://www.epa.gov/oppt/newchems/tools/manual.pdf)

Read-Across/Data Bridging

- **Endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be "similar" based on:**
  - Structural similarity
  - Similar mode of action (MOA)

- **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 (*i. e.*, organophosphate pesticides)

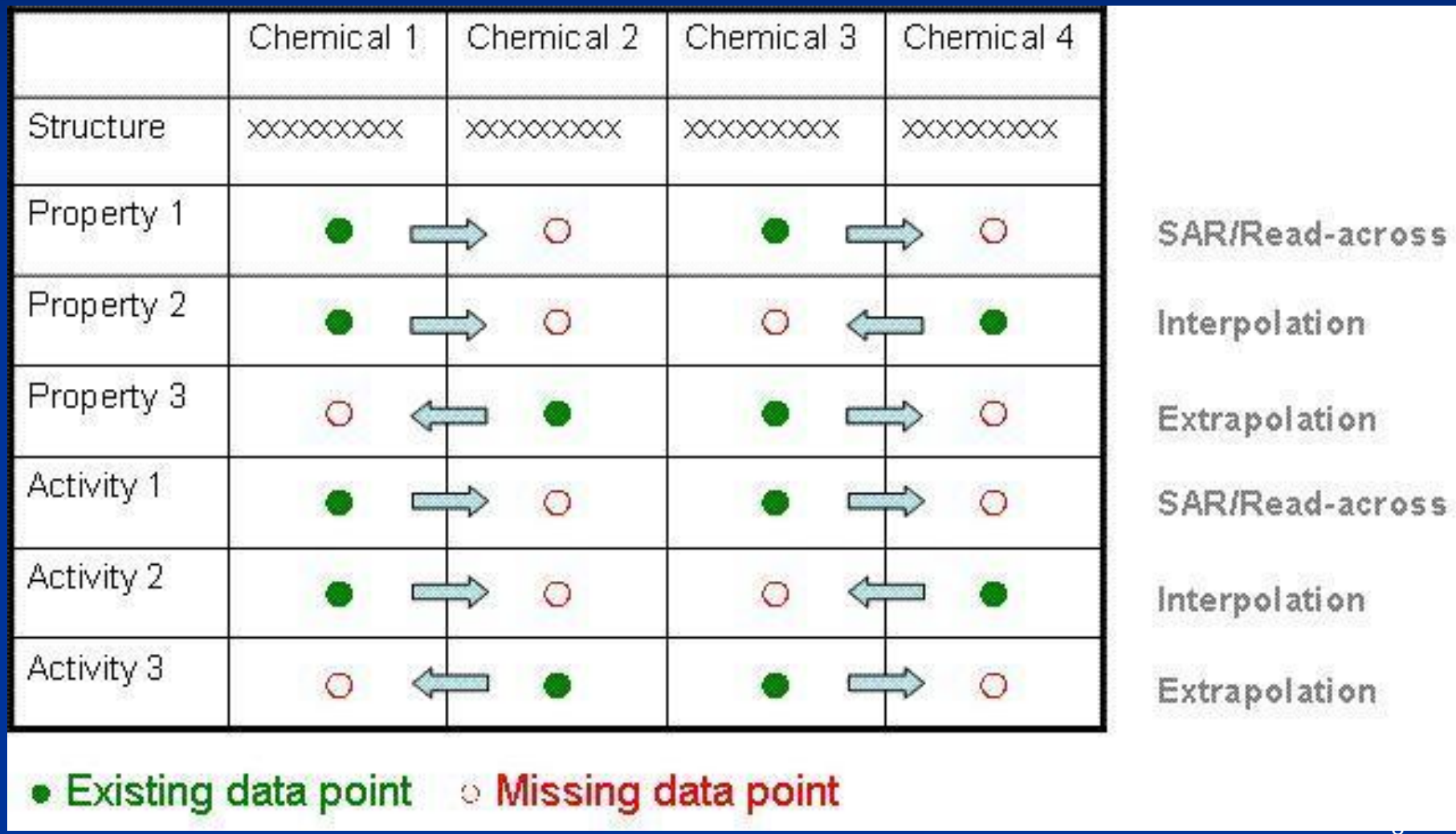
OECD-EPA Chemical Categories

- **A chemical category is a group of chemicals whose physicochemical and human health and/or ecotoxicological properties and/or environmental fate and properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity**

- **The similarities may be based on:**
  - a common chemical functional group
  - similar carbon range numbers – *i.e.*, C6 or C8
  - Physicochemical properties – *i.e.*, boiling point
  - Common precursors and/or degradates

- **Data gap filling in a chemical category can be achieved by applying one or more of the following procedures: read-across, trend analysis, and (Q)SARs**

Chemical Category Matrix Table



Mode of Action (MOA)

- **MOAs serve to describe how a particular chemical or chemical group acts to kill or disable insects, noxious plants, or fungi through specific interaction (activity) with a target within the plant or animal**
- **Each group of insecticides and fungicides has associated with it a particular mode of activity or mode of action.**
- **Potential Utility of MOA**
  - Use of MOA within [Q]SAR, read-across, SSD models
  - Target species MOA vs. non-target species MOA
  - Adverse outcome pathways and how MOA ties into them

Acute-to-Chronic Ratios (ACR)

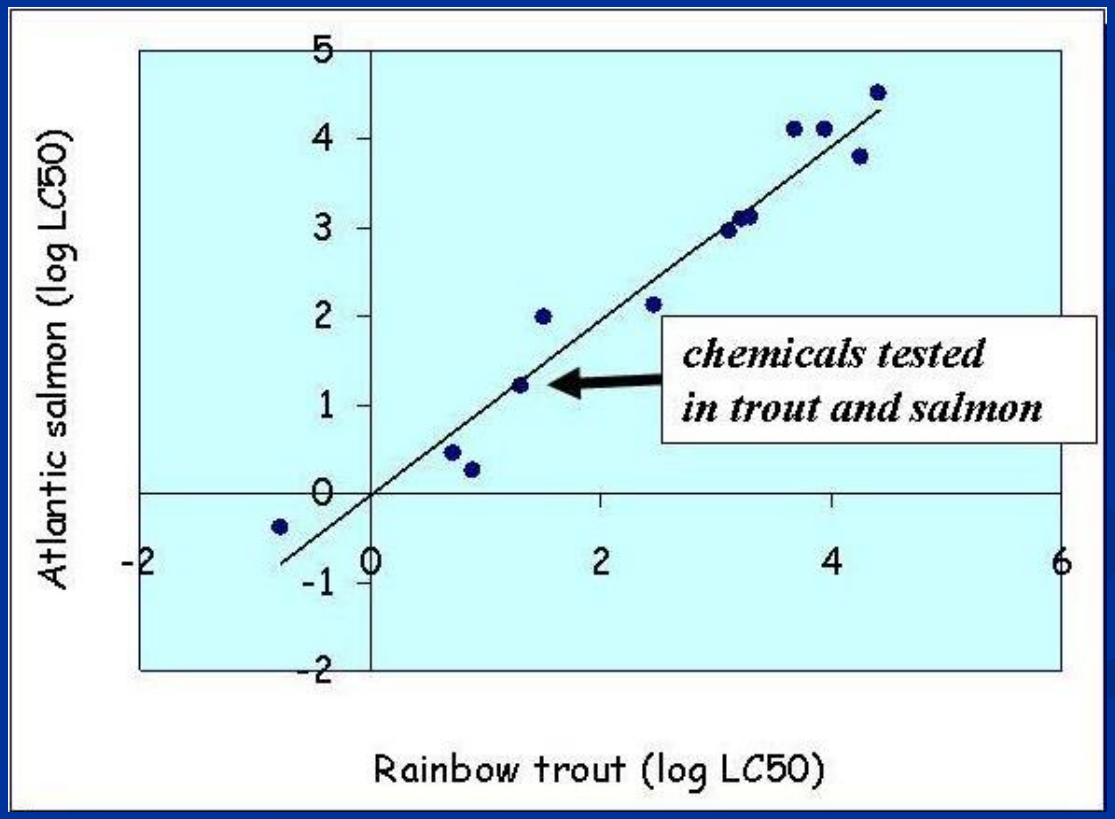
- Used to estimate chronic toxicity in aquatic organisms for which acute toxicity is known, but chronic data are limited or absent
- ACR = ratio of LC_{50} or EC_{50} to chronic NOAEC or MATC (geometric mean of NOEC and LOEC)
- OPP uses ACRs when acute toxicity profile indicates that the most sensitive surrogate aquatic species was not tested in chronic study or data gaps exist
- OW uses ACRs routinely when insufficient data are available to calculate a Final Chronic Value (FCV) containing 8 families as defined by the 1985 Guidelines (≥ 3 chronic tests) – calculate FACR

Interspecies Correlation Models (ICE)

- **Interspecies extrapolation models**
- **Estimates acute toxicity (LC_{50} or EC_{50}) for a species, genus or family from a surrogate species**
- **Uses of ICE in ecological effects assessment**
  - Populates toxicity database
  - Allows for species sensitivity comparisons
  - Direct toxicity estimation for endangered species
  - Quantifiable model confidence

Interspecies Correlation Models

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



Interpretation Framework For Predictive Tools

- **Using OECD validation principles as a framework for guidance ([Q]SAR)**
  - 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

- **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

Summary

- Through this White Paper, the Agency (OW, OPP, ORD) will present an overview of predictive tools that may be useful in generating data for use in effects assessment and derivation of aquatic community-level benchmarks
- Goals:
  - More consistent and uniform use of predictive tools toward estimating and accounting for sensitivity of non-target organisms to pesticides
  - Increased transparency and consistency in effects characterization between OPP and OW