END USER APPLICATIONS: OECD LANDSCAPE

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PREDICTIVE MODELS FOR ACUTE ORAL SYSTEMIC TOXICITY WORKSHOP
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OECD WORKING PRINCIPLES

• Everything requires consensus
• Treaty on Mutual Acceptance of Data
  • Applies to protocols, not interpretations
  • Does not preclude counties from asking for more
• Work towards harmonization in interpretation/classification
• Saves countries’ resources
• “Learn by doing” approach
OECD FUNCTIONS

• Test Guidelines
  • Adopts test guidelines for generating hazard characterization data according to country needs and via expert working groups
  • Writes accompanying guidance and validation reports

• Hazard Assessment
  • History of cooperative assessments, read across, now IATA case studies
  • Harmonized templates, data recording tools
  • Tools for hazard assessment and management of chemicals for developing countries

• Administers AOP Programme
  • Tools for recording AOP information
  • Series on AOPs: endorsed jointly
OECD AND QSAR: LONG HISTORY OF COOPERATION

• 1992: Report of the OECD Workshop on Quantitative Structure Activity Relationships (QSARs) in Aquatic Effects Assessment

• Report on the Regulatory Uses and Applications in OECD Member Countries of (Q)SAR Models in the Assessment of New and Existing Chemicals, No. 58 (2006)

• March 2008: First release of the OECD QSAR Toolbox
  • Intended to provide tools for regulatory use
  • Databases, grouping/category formation, read across, profilers, metabolism predictors

• Guidance Document for using the OECD (Q)SAR Application Toolbox to develop Chemical Categories according to the OECD Guidance on Grouping of Chemicals, Series on Testing and Assessment No. 102, (2009)
  • Many training materials created/offered since
  • Webinars, hands-on training as well

• Additional updated/new documents related to QSAR available

• Toolbox version 4.2 released Feb 2018
A validated (Q)SAR is a model considered to be reliable for a particular purpose based on the results of the validation process in which the domain of application and the level of uncertainty required is defined.

A valid (Q)SAR is a model considered to be adequate for the intended purpose either because reliability has been demonstrated by historical use or by a validation process.

To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1) a defined endpoint
2) an unambiguous algorithm
3) a defined domain of applicability
4) appropriate measures of goodness-of-fit, robustness and predictivity
5) a mechanistic interpretation, if possible

Interpretation Guidance for principles

QSAR Method Reporting Format
FACILITATING REGULATORY ACCEPTANCE

• Understand what is needed
• Explain decisions you have made
• Documentation and transparency
• Offer hands-on training
• Demonstrate how your tool meets their needs
• Be sure you are reflecting the chemistries of concern
• Use case studies
• Mechanistic relevance increases trust
• Use pictures!

What do we mean by regulatory acceptance?
Recent OECD QSAR Toolbox Additions

- Automated workflows for certain endpoints
- Initially controversial
- For frequent endpoints such as fish acute toxicity, skin sensitization
- Demonstrates the prediction to allow novices to gain experience and document steps/results

Database Reliability scores

- Accuracy (format, qualifiers, scales)
- Completeness (substance completeness and metadata variation)
- Contemporaneity (distribution by year)
- Consistency (substance consistency and substance type profile)
BASIC IATA

- Test Guidelines
- “Non-guideline” methods (GD 211)
- Integrated Testing Strategies
- QSARs
- Read Across
- Defined Approaches
- Modeling results
- “Information”

No. 270: REPORT ON CONSIDERATIONS FROM CASE STUDIES ON INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT (IATA)

- Demonstrates general lessons on how to increase acceptance of and confidence in read across predictions
- Demonstrates use of transcriptomic and ToxCast data to facilitate prediction or reduce uncertainty
- Specific examples of reduced uncertainty

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Title</th>
<th>Type of Assessment</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>2017</td>
<td>1</td>
<td>Estrogenicity of Substituted Phenols</td>
<td>Prioritization and hazard characterization</td>
<td>Endocrine disruption</td>
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<td>Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification</td>
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<td>Case study on grouping and read-across for nanomaterials genotoxicity of nano-TiO2</td>
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<td>A Case Study on the Use of Integrated Approaches for Testing and Assessment for Sub-Chronic Repeated-Dose Toxicity of Simple Aryl Alcohol Alkyl Carboxylic Esters: Read-Across</td>
<td>Grouping (Read-across)</td>
<td>Repeated dose toxicity</td>
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<td>Repeated-Dose Toxicity of Phenolic Benzotriazoles</td>
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<td>Pesticide Cumulative Risk Assessment &amp; Assessment of Lifestage Susceptibility</td>
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<td>90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across</td>
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<td>Repeated dose toxicity</td>
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<td>90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across</td>
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<td>Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-animal Methods</td>
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<td>In Vitro Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes</td>
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WHAT IS A DEFINED APPROACH?

• Defined information sources
  • Experimental methods
  • Characteristics
  • Predictions
• Fixed data interpretation procedure
  • Algorithm for interpreting data
  • Manual or automated
• Offers potential for mutual acceptance of in silico predictions via DA TG
THANK YOU FOR YOUR ATTENTION!

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