Development of Read-Across for Chemical Safety Assessment

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Concurrent Session 3 Resource Document
Challenges in Read-Across and Building Confidence for Use in Decision Making

Co-Chair: Richard Becker, American Chemistry Council, USA
Co-Chair: Ayako Takei, ICaRuS Japan Limited, Japan

- Takashi Yamada, NIHS, Japan
- Yuki Sakuratani, OECD, France
- Volker Koch, Clariant, Germany
- Renjun Gao, Dow, China

- Jongwoon Kim, KIST, Korea
- Yutaka Ikenaga, NITE, Japan
- Sharon Buring Stuard, P & G, USA
- Ivan Rusyn, Texas A & M, USA

*International Council of Chemical Associations’ Long-Range Research Initiative*
Read-across is regarded as a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s) (source substance(s)).

Biodegradation in active sludge (BOD: Biological Oxygen Demand)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Target substance</th>
<th>Source substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biodegradation</td>
<td>BOD: &gt;50% Readily degradable (Read-across)</td>
<td>BOD: 74% (Measured) Readily degradable</td>
</tr>
</tbody>
</table>
Read-across saves resources and animals

Not a new concept, but gains importance
- as the number of assessed chemicals increase
- animal welfare gains importance

OECD Guidance, strongly emphasized in REACH Guidance
Terminology

- Category approach and analogue approach
  - Techniques for grouping chemicals

- Read-across
  - Technique of filling data gap in either approach

Target chemical

Category approach

Tested analogue

Grouping chemicals

Read-across

Data gap filling
  (Estimate endpoint information)
ECHA Process for Read-Across Evaluation

- Preparatory assessment
  - Identity of target chemical
  - All required elements for read-across
    - Hypothesis
    - Justification
    - Data matrix
    - Conclusion of read-across

- Scientific assessment
  - Scientific explanation to judge the validity of the read-across
REACH Registration (repeated-dose toxicity)

The Use of Alternatives to Testing on Animals for the REACH Regulation (2014)

<table>
<thead>
<tr>
<th>RDT – all routes, all study durations (HH)</th>
<th>No. ESR</th>
<th>% ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>2411</td>
<td>24.6</td>
</tr>
<tr>
<td>TP</td>
<td>227</td>
<td>2.3</td>
</tr>
<tr>
<td>RA</td>
<td>3220</td>
<td>32.9</td>
</tr>
<tr>
<td>FO</td>
<td>2435</td>
<td>24.9</td>
</tr>
<tr>
<td>WE</td>
<td>1372</td>
<td>14.0</td>
</tr>
<tr>
<td>QS</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>MS</td>
<td>85</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>9786</td>
<td>100</td>
</tr>
</tbody>
</table>

**Legend:**
- ESR – Endpoint Study Record
- ES – Experimental studies
- TP – Testing proposal
- RA – Read-across
- FO – IUCLID flags to omit the study
- WE – Weight of Evidence approach
- QS – (Q)SAR studies
- MS – Miscellaneous
Regulatory Acceptance of Read-Across in Asian Countries

- Japan
  - Industrial chemical (CSCL): accepted for biodegradation and bioaccumulation. Being discussed for other endpoints

- China
  - New chemical, food additive, pharmaceutical excipient, pesticide, in general-NO
  - Cosmetic raw material: in general-NO

- Korea
  - Industrial chemical (K-REACH): in general-NO
HESS: A tool to find analogues and the repeated-dose toxicity tested data for read-across

Findings

Target chemical

Tested analogs

RDT test data (NOEL/LOEL)

Data gap

Link

Possible category

Link to Metabolism/Mechanistic Information and Toxicity Test Results of Analogues

Metabolism

Form mechanism-based category

MoA/AOP

Confirm the test data of the nearest analogue for read-across

Toxicity test results
OECD QSAR Toolbox

- Free software to support data gap filling by category approach (http://www.qsartoolbox.org/)
- Tools for finding analogues and test data for regulatory endpoints are included.
QSAR Toolbox: Databases and Profilers for Human Health Hazard

Databases

- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards
  - Bacterial mutagenicity ISSSTY
  - Carcinogenic Potency Database (CPDB)
  - Carcinogenic & mutagenicity ISSCAN
  - Cell Transformation Assay ISSCTA
  - Dendritic cells COLIPA
  - Developmental & Reproductive Toxicity (DART)
  - Developmental toxicity ILSI
  - ECHA CHEM
  - ECOTOX
  - Estrogen Receptor Binding Affinity OASIS
  - Eye Irritation ECETOC
  - Genotoxicity OASIS
  - Human Half-Life
  - Keratinocyte gene expression Givaudan
  - Micronucleus ISSMIC
  - Micronucleus OASIS
  - MUNRO non-cancer EFSA
  - Rep Dose Tox Fraunhofer ITEM
  - Repeated Dose Toxicity HESS
  - Rodent Inhalation Toxicity Database
  - Skin Irritation
  - Skin Sensitization
  - Skin sensitisation ECETOC
  - Toxicity Japan MHLW
  - ToxRefDB US-EPA
  - Yeast estrogen assay database

Profilers

- Bacterial mutagenicity, Carcinogenic potency, Cell transformation, Developmental and reproductive toxicity, Genotoxicity etc.
- Repeated dose toxicity

Repeated dose toxicity

RepDose

HESS
Company IUCLID DB & ECHA IUCLID DB as Major Data Sources

Transfer via Web service or *.i5z files

LRI AMBIT Supporting Read across & Category formation

Transfer of 14570 Dossiers

Other Databases

Data transfer

Data transfer

Tools

Data transfer
**Analogue Read-Across with CBRA**

Integrative Chemical–Biological Read-Across Approach for Chemical Hazard Classification

Yen Liew, Alexander Sedykh, Denis Fournier, Alexander Golbraikh, Maurice Whelan, Ivan Rusyn, and Alexander Troshin

**Category Read-Across with ToxPi**

**BIOINFORMATIC APPLICATIONS NOTE**

ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence

David M. Reid, Myrsiav Syzga, Eric F. Lock, Fred A. Wright, Andrew Wilson, Tommy Cahery, Richard R. Judson, and Ivan Rusyn

Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data


National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; Office of Science Coordination and Policy, Office of Pollution Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C., USA
OECD IATA Case Studies Project (2015-)

- IATA (Integrated Approaches to Testing and Assessment)
- Combinations of in silico, in chemico, in vitro approaches. Read-across is a part of IATA.
- Provide a forum to increase experience with the use of IATA for regulatory purpose
- Develop guidance
- Project team: Australia, Canada, Denmark, Japan, Netherlands, Sweden, United States, EU (EC), EU (JRC), EU (ECHA), BIAC and ICAPO

Case Studies (2015)

- In Vitro Mutagenicity of 3,3’ Dimethoxybenzidine (DMOB) based Direct Dyes [Canada & US]
- Repeated Dose Toxicity of Substituted Diphenylamines (SDPA) [Canada]
- Hepatotoxicity of Allyl Ester Category [Japan]
- Bioaccumulation Potential of Biodegradation Products of 4,4’-Bis (chloromethyl)-1,1’-biphenyl [Japan]

All the case studies illustrate pragmatic use of grouping methods while addressing some challenging topics such as the use of AOP information.

Just released!

First Four Case Studies from the Integrated Approaches to Testing and Assessment (IATA) Case Studies Project

The first four case studies from the IATA Case Studies Project were published along with a reporting template and considerations document highlighting the learnings from the first review cycle.

The IATA Case Studies Project was launched in 2015 to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use.

October, 2016
Case Study Developed by JP (2015)

Allyl ester → Allyl alcohol → Acrolein (Readily activated in the liver)

Hepatotoxicity

Metabolic hydrolysis: critical key event directly linked to the primary adverse outcome

NOAEL = 0.25 mmol/kg/d

Allyl alcohol

NOAEL = 0.10 mmol/kg/d

Acrolein (Readily activated in the liver)

NOAEL = 0.44 mmol/kg/d

Source chemical

Empirical metabolism data available

Primary toxicity of the category: hepatotoxicity

Presumed NOAEL: 0.1 mol/kg bw/day
Reviewers’ Comments for the JP Case Study in 2015

- Is a selected analogue the nearest among the category member?
- Justify structural differences may not cause different toxicity
- Define structural boundary of the category
- Assess confidence of test data used for read-across
- Avoid underestimating toxicity level of a target substance
- Describe human relevance
- Identify uncertainties and quantify the levels/its regulatory acceptance
Definition of analogues/category boundaries

- Lacked a discussion on the structural differences whereas their structural similarities were well documented.

Uncertainty analysis and reporting

- Each case study contains different uncertainties because of limited data or resource.
- Uncertainty analysis helps reviewers to consider the acceptable degree of uncertainty to the specified purposes.
Read-across methodologies are currently valuable for optimizing allocation of limited resources and expediting chemical safety assessments.

While current procedures have intensified focus on quality data, explicit documentation, and specific justification, there is a lack of globally accepted methods to evaluate uncertainties associated with predictions.

The biggest barriers to widespread application of read-across are insufficient documentation of validation, limited number of successful case studies, lack of globally recognized guidelines and limited number of regulators with experience in read-across etc.
Future research should address uncertainty and variability in read-across, and prediction of ADME and toxicokinetics for target substances. There is a strong need for high quality databases for source chemicals.

In order for the data from new and alternative methods (Tox21, omics, ToxCast, AOPs, etc.) to be used, there is a need for education and outreach to enhance regulators’ understanding of these new data streams and biological profiling approaches. These efforts should also plan for upcoming challenges, such as complex products and mixtures.
Thank you very much for your attentions!