Best Practices for Addressing Human Health and Environmental Data Gaps in an Alternatives Assessment Context

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OVERVIEW

- HESI Project Background
- Guidance Framework
- Case Study
- Looking to the Future of Safer Products/Processes
- Q & A
HESI Sustainable Chemical Alternatives Committee

- Technical committee established to develop practical, problem-driven guidance on the conduct of alternative chemical assessment.
- Collaborative effort of academia, government, industry, and non-profit organizations
- Project objectives
  - Identify strengths, weaknesses and gaps in current approaches.
  - To identify emerging needs/challenges for the future
  - More detailed guidance to help key stakeholders through the alternatives assessment process
  - Address different needs across the supply chain
  - Help facilitate new product development
### Issue: Lack of Critical Hazard Information

#### CHALLENGES
- Weighing one chemical against another?
  - Alternatives often have less information or profile is different compared to established products
- Minimum base data set?
  - Need the information that will discriminate between two options.
  - Are there scenarios where you can eliminate the need for certain data?
- How will you get data or fill data gaps?
- Best practices, scientifically robust, vetted methods?
  - Utility of emerging tools/technologies

#### OPPORTUNITIES
- Develop specific guidance that:
  1. Takes into consideration stage of product development – drive innovation
  2. Focuses on critical information needs
  3. Leverages predictive tools & technologies
  4. Weight of evidence approach
Concept: Stage Gate Process to Filling Data Gaps

- **Concept**
  - Identify/define new product concepts

- **Feasibility**
  - Assess commercial/technical feasibility

- **Development**
  - Pilot manufacturing/meet market requirements

- **Commercialization**
  - Scale up manufacturing; pass regulatory requirements

- **Launch**
  - Launch products in target markets/geographies

- **Post Launch**
  - Monitor through end of life cycle

**Decision Gates**

**Existing information, Read Across**

- Computational Modeling (Q)SARs,
- In vitro biological profiling
- Targeted animal studies
Apply Tiered Assessment Approach

**Tier 1 - Cheminformatics**

Tools: Data mining, Analog ID, Read across, QSAR, (internal and publically available data)

**Tier 2 – In Vitro Biological Profiling**

In vitro predictive assays (selected based on specific question/need)

**Tier 3 – Standard Regulatory Toxicology**

Test guidelines (selection based on regulatory need)
Framework: Integrated Approaches to Testing and Assessment (IATA)

Problem Formulation:
Identification of the data gap & minimal test battery throughout stage gate process

Gathering of Existing Information:
Cheminformatics, QSAR, read-across, chemical category, database searching, etc.

Weight-of-Evidence Assessment:
Adequate Information for endpoint hazard assessment?

Generation of Additional Data:
in chemico, in vitro, ex vivo, HTS, -omic,
guideline in vitro/in vivo testing, etc.

New Weight-of-Evidence Assessment:
Adequate Information for endpoint hazard assessment?

Endpoint Hazard Conclusion/Classification

YES
NO

YES
NO

YES
Non-testing Approaches to Fill Data Gaps

• **Read-across**: Endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be similar in some way (usually, based on structural similarity or same mode of action)

• **Trend analysis**: Refers to a data-gap filling method for “quantitative endpoints” (e.g., 96h-LC50 for fish) if a number of analogues (at least 3) with experimental results are identified (OECD 2014)

• **(Q)SAR (Quantitative Structure Activity Relationship)**: Commonly used to address data gaps for physicochemical properties such as log Kow, environmental fate (biodegradation, hydrolysis, bioaccumulation potential), ecotoxicity (acute aquatic toxicity), mammalian toxicology (such as mutagenicity, sensitization, and carcinogenicity)
Case Studies
# N-Propyl Acrylate

<table>
<thead>
<tr>
<th>Example of Data Gap Filling (select endpoints) using non-testing tools</th>
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</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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</tbody>
</table>

**Determine background information, such as structure, use, and initial modeling**

- n-Propyl Acrylate (CASRN: 925-60-0)
- IUPAC Name: propyl prop-2-enoate
- Smiles: C(=O)(OCCC)C=C
- Molecular Formula: C<sub>6</sub>H<sub>10</sub>O<sub>2</sub>
- Molecular Weight: 114.15 g/mole

PubChem (2017) describes n-Propyl Acrylate (CID 13550) as a monomer utilized in the synthesis of emulsion polymers, solution polymers and acrylic fibers with applications in latex paints, textile applications, polishes, paper applications, base coatings and surface impregnation of natural leather, as well as in other miscellaneous applications.

**Toxic Classification by Cramer:**
- Extension: High (Class III)
- Original: Low (Class I)
- Lipinski Rule Oasis: Bioavailable
## N-Propyl Acrylate: Skin Sensitization

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>Skin</th>
<th>PLAUSIBLE</th>
<th>DEREK Nexus v.5.0.2</th>
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</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Parent (+)</td>
<td>Metabolites (-) (Relevant)</td>
<td>OASIS TIMES V.2.27.20</td>
</tr>
<tr>
<td>Skin</td>
<td>&quot;Allergic Contact Dermatitis in Guinea Pig and Human&quot;: POS_IN (i.e. positive &amp; inside the applicability domain).</td>
<td></td>
<td>Danish CASE Ultra module</td>
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<td>Danish Battery module</td>
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<td>Danish Leadscope, SciQSAR module</td>
</tr>
</tbody>
</table>

### Overall Skin Sensitization Summary:
The WoE assessment based on the read-across and in silico data indicates skin sensitization potential with high confidence; skin sensitization category 1 H317: May cause an allergic skin reaction is proposed for N-Propyl Acrylate.
N-Propyl Acrylate: Acute Toxicity

Overall Acute Toxicity Summary: The WoE assessment based on the read-across combined with in silico (Q)SAR and trend analysis indicates acute toxicity LD50 values of < 2,000 mg/kg with medium confidence. n-Propyl Acrylate is expected to have an acute oral GHS category 4; H302: Harmful if swallowed and an acute dermal GHS 4, H312: Harmful in contact with skin classifications. Finally, acute inhalation GHS category 3, H331: Toxic if inhaled is proposed for n-Propyl Acrylate.
Looking into the Future of Alternative Assessments

- Evolving in silico technologies will greatly enhance the ability to fill gaps in critical hazard data.
- Continued guidance and structure are needed to ensure consistency & robustness of application/interpretation of in silico data.
- A4 will be a key organization to guide the evolution and application of new technologies in alternatives assessment.
Vision – Backward or Forward Looking?

Where we’ve been . . .
• AA’s to ID safer existing chemicals
• Data gaps treated in inconsistent ways; often had to default to most conservative assessment when lacking data
• Sparse guidance on specifics of AA

Where we can go . . .
• Formalize approaches to filling data gaps
• Conduct AA throughout product development process
  ✓ Design for safety
  ✓ Drive innovation
• Standardize hazard assessment training in toxicology programs
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