Case study from SEURAT-1
β-Olefinic alcohols: indirect acting toxicant category supported by SEURAT-1 data

Read-Across Case Study Considered in Context of the ECHA RAAF

Andrea Richarz, EC JRC, IHCP
The β-Olefinic Alcohols Case Study: Premise

- Short chain (C3 to C6) unsaturated alcohols are indirect-acting toxicants
- Same covalent mechanism of action and similar reactive potency
- Metabolism via alcohol dehydrogenase (ADH)
- Metabolites are electrophilic with in vivo potency related to relative thiol reactivity
β-Olefinic Alcohols: Category Members

Source substance:
90 day NOAEL read across from 2-propen-1-ol (worst case); NO(A)EL driven by liver toxicity

Chemical structures of various β-olefinic alcohols.
The ECHA Read-Across Assessment Framework (RAAF) Approach

Scientific Assessment of Read-across argument according to scenarios defined by 3 key features:

# of substances considered:
• Analogue approach – one source and one target
• Category approach – multiple source(s) and target(s) (group)

Effect (predicted property) caused by:
• common substance for source(s) and target(s)
• different substances for source(s) and target(s)

For a Category, the predicted property:
• Follows a regular pattern (trend) across source structures
• Does not change across source structures

→ 6 Possible read-across Scenarios
Scientific Assessment of Read-across argument according to scenarios defined by 3 key features:

**Possible Scenarios:**

- **# of substances considered:**
  - Analogue approach / one source and one target
  - Category approach / multiple source(s) and target(s) (group)

- **Effect (predicted property) caused by:**
  - Common substance for source(s) and target
  - Different substances for source(s) and target

For a Category, the predicted property:

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→ 6 Possible Read-Across Scenarios
The ECHA Read-Across Assessment Framework (RAAF) Approach

Scientific Assessment of Read-across argument according to scenarios defined by 3 key features:

# of source chemicals:

**β-Olefinic Alcohols →**

Scenario #4, category approach: different compounds with same type of effect, difference in effect strength

For a Category, the predicted property:

- Follows a regular pattern (trend) across source structures
- Does not change across source structures

→ 6 Possible Read-Across Scenarios
The RAAF: Assessment Elements and Assessment Options

Set of **Assessment Elements (AE's)** per Scenario

- Describing ‘crucial scientific aspects to judge validity and reliability of read-across for the Scenario’
- For each AE multiple considerations to be included in justification

**Assessment Options (AO's):**

- Reflect the conclusion on adequacy and scientific robustness of the information provided for the AE
- **Scores from 5 to 1**
  - $\geq 3$ : information provided is **acceptable** with just (3) sufficient, (4) medium, (5) high confidence
  - $\leq 2$ : information provided is (1) **not acceptable**,
    (2) not acceptable in its current form
The RAAF: Assessment Elements

General (Common) Assessment Elements

C.1 Substance characterisation
C.2 Structural similarity and category hypothesis
C.3 Link of structural similarities and structural differences with the proposed regular pattern
C.4 Consistency of effects in the data matrix - order within category/clustering of strength of effects
C.5 Reliability and adequacy of the source study(ies)
C.6 Bias that influences the prediction

Scenario-Specific Assessment Elements: Scenario #4
different compounds with same effect, difference in effect strength

4.1 Compounds the test organism is exposed to
4.2 Common underlying mechanism, qualitative aspects
4.3 Common underlying mechanism, quantitative aspects
4.4 Exposure to other compounds than to those linked to the prediction
4.5 Occurrence of other effects than covered by the hypothesis
### βOA Case Study Considered with the RAAF

<table>
<thead>
<tr>
<th>AE</th>
<th>Subst. characterisation</th>
<th>Structural similarity</th>
<th>Link structures and regular pattern</th>
<th>Consistency effects in data matrix; clustering</th>
<th>Reliability/adequacy source study(ies)</th>
<th>Compounds the organism is exposed to, transformation</th>
<th>Common mechanism, qualitative aspects</th>
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<th>Exposure to other compounds</th>
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<th>Bias influencing prediction</th>
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</table>

**Remaining questions**

- Similarity and category boundaries
- Metabolism mechanism, exclude other than ADH
- More details in vivo studies
- Confirm subcategory reactivity trends
- More details on study design and quality
- More (quant.) information: rate/speed of metabolism
- Strengthen proof that source substance is the worst-case
- More details (quant.) kinetics: residual parent/further metabolites & effects
- Rule out other effects / metabolic mechanisms
- Read-across valid for other structural variation members?
RAAF I: Category and Structural Similarity

Identity (C.1)/ Structural Similarity / (Not) Allowed Differences (C.2)/ Link Structures and Effect Pattern (C.3) / Choice of Compounds (Bias) (C.6)

Complexity of the structural variations

- Two scaffoldings: **primary** (external –OH) / **secondary** (internal –OH)
- External or internal vinyl group
- Structural similarity complicated by alkyl substituents on the allylic moiety
  → **straight-chained or branched**
**β-Olefinic Alcohols Subcategories**

- **Primary Alcohols**
- **Secondary Alcohols**

Two scaffoldings
β-Olefinic Alcohols Subcategories

External or internal vinyl group

Primary Alcohols

Secondary Alcohols
β-Olefinic Alcohols Subcategories

Straight-chained Alcohols

Branched Alcohols
RAAF I: Category and Structural Similarity

Identity (C.1) / Structural Similarity / (Not) Allowed Differences (C.2) / Link Structures and Effect Pattern (C.3) / Choice of Compounds (Bias) (C.6)

Complexity of the structural variations

• → Similarity / Inclusion in category /
  How broad or narrow should a category be?
  Not included: acetylenic alcohols (metabolism difference)

• → Category valid for other structural variations?

• → Parent structure determines metabolite formed
  → Different reactivity metabolites → potency of effects
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Complexity of the structural variations

- Similarity / Inclusion in category / How broad or narrow should a category be?
  - Not included: acetylenic alcohols (metabolism difference)
- Category valid for other structural variations?
- Parent structure determines metabolite formed
- Different reactivity metabolites = potency of effects

Existing NAM ex vivo liver perfusion:

- Shows reactivity for different structural variants of βOAs ≠ alkanols
RAAF II: Metabolic Transformation to Toxicants

Link Structures and Effect Pattern (C.3) / Compounds to Which Organism Exposed (4.1) / Exposure to Other Compounds? (4.4)

Metabolites are the definitive toxicants

\[
\text{RCH(C=CH)C=CH}_2 \xrightarrow{\text{ADH}} \text{RC(=CH)C=CH}_2
\]

\[
\text{RC(=CH)C(=CH)R} \xrightarrow{\text{ADH}} \text{RC(=CH)C(=CH)O}
\]

\[\alpha,\beta\text{-unsaturated aldehyde}\]

\[\alpha,\beta\text{-unsaturated ketone}\]
RAAF II: Metabolic Transformation to Toxicants

**Link Structures and Effect Pattern (C.3) / Compounds to Which Organism Exposed (4.1) / Exposure to Other Compounds? (4.4)**

**Metabolites are the definitive toxicants**

- Mechanism and kinetics of transformation → any other than metabolism by ADH?

- **Further metabolism pathway of aldehydes and ketones different → metabolic similarity?**
  → more quantitative kinetics information needed, relative efficiency of biotransformation → residual parents, further metabolites present with possible reactivity?
RAAF II: Metabolic Transformation to Toxicants

Link Structures and Effect Pattern \((C.3)\) / Compounds to Which Organism Exposed \((4.1)\) / Exposure to Other Compounds? \((4.4)\)

Metabolites are the definitive toxicants

- Mechanism and kinetics of transformation and toxification internally? Why not ADH?
- Further metabolism pathway of aldehydes and ketones different metabolite similarity? More quantitative kinetics information needed, relative efficiency of biotransformation residual parents, further metabolites present with possible reactivity?

Existing NAM ex vivo liver perfusion and \textit{in silico}:

- Link toxicity to metabolic transformation
- Electrophilic reactivity aldehydes/ketones

Also confirmed by SEURAT-1 hepatic organoids
RAAF III: Available \textit{(In Vivo)} Data

Consistency Data Matrix (C.4) / Reliability and Adequacy of \textit{(In Vivo)} Data (C.5) / Choice of NOAEL to Read Across

Details and quality of \textit{in vivo} studies

\begin{tabular}{|p{\textwidth}|}
\hline
\textbf{NTP study used for read-across} \\
\hline
Rats and Mice: NOAEL 6 (m) and 25 (f) mg/kg bw/d for rats. Relating to toxicity in the liver. \\
\hline
\end{tabular}
RAAF III: Available (In Vivo) Data

Consistency Data Matrix (C.4) / Reliability and Adequacy of (In Vivo) Data (C.5) / Choice of NOAEL to Read Across

Details and quality of in vivo studies

• More information on study design and quality needed → selection of NAOEL to read across

• → guidance/ specific matrix needed for providing study details for RAAF?

• → also for NAM: how to evaluate new assay quality?
RAAF III: Available *(In Vivo)* Data

Consistency Data Matrix (C.4) / Reliability and Adequacy of *(In Vivo)* Data (C.5) / Choice of NOAEL to Read Across

Details and quality of *in vivo* studies

- More information on study design and quality needed
- → selection of NOAEL to read across
- guidance/specific matrix needed for providing
- overall existing and SEURAT-1 NAM *in vivo / in vitro / in silico* data
- give a consistent picture *(differences in strength of effects)*
- → also for NAM: how to evaluate new assay quality?
RAAF IV: Mechanism of Toxicity

Mechanism of toxicity (qualitative) (4.2) / Other effects? (4.5)

Electrophilic reactivity (Michael addition mechanism), binding to proteins → adverse effects
RAAF IV: Mechanism of Toxicity

Mechanism of toxicity (qualitative) (4.2) / Other effects? (4.5)

Electrophilic reactivity (Michael addition mechanism), binding to proteins → adverse effects

- More information needed (also kinetics) to exclude any other mechanisms (by other compounds present)
- Hypothesis of fibrosis as adverse effect

AOP for Liver Fibrosis (from Landesmann et al 2012)
RAAF IV: Mechanism of Toxicity

Mechanism of toxicity (qualitative) (4.2) / Other effects? (4.5)

Electrophilic reactivity (Michael addition mechanism), binding to proteins → adverse effects

In silico/in chemico/SEURAT-1 in vitro NAM
(hepatic organoids with HSC activation markers; stress response activation in HepG2) add mechanistic plausibility,
in particular the HSC activation markers strengthen the hypothesis of MoA leading to fibrosis (not supported by rat data)
Clustering of potency of effects according to chemical reactivity

- Quantitative reactivity data only from *in chemico* GSH assay supported by *in silico* predictions
## Reactivity In Chemico and In Silico

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Compound</th>
<th>Metabolite</th>
<th>In Chemico reactivity GSH RC50(^1)</th>
<th>Protein binding potency (^2)</th>
<th>In silico protein binding (^2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>2-propen-1-ol</strong></td>
<td>2-Propenal (acrolein)</td>
<td>0.085</td>
<td>Extremely reactive</td>
<td>MA, SBF</td>
</tr>
<tr>
<td>2</td>
<td><strong>2-buten-1-ol</strong></td>
<td>2-Butenal (crotonaldehyde)</td>
<td>0.22</td>
<td>Highly reactive</td>
<td>MA, SBF</td>
</tr>
<tr>
<td>3</td>
<td><strong>2-penten-1-ol</strong></td>
<td>trans-2-Pentenal</td>
<td>0.35</td>
<td>Highly reactive</td>
<td>MA, SBF</td>
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<td>4</td>
<td><strong>2-hexen-1-ol</strong></td>
<td>trans-2-Hexenal</td>
<td>0.42</td>
<td>Highly reactive</td>
<td>MA, SBF</td>
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<tr>
<td>5 Straight chain</td>
<td><strong>1-butene-3-ol</strong></td>
<td>Methyl vinyl ketone</td>
<td>0.070</td>
<td>Extremely reactive</td>
<td>MA</td>
</tr>
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<td>6</td>
<td><strong>1-penten-3-ol</strong></td>
<td>Ethyl vinyl ketone</td>
<td>0.051</td>
<td>Extremely reactive</td>
<td>MA</td>
</tr>
<tr>
<td>7</td>
<td><strong>1-hexen-3-ol</strong></td>
<td>Propyl vinyl ketone</td>
<td>0.059</td>
<td>Extremely reactive</td>
<td>MA</td>
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<td>8</td>
<td><strong>3-penten-2-ol</strong></td>
<td>3-Penten-2-one</td>
<td>0.15</td>
<td>Highly reactive</td>
<td>MA</td>
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<td>9</td>
<td><strong>3-hexen-2-ol</strong></td>
<td>3-Hexen-2-one</td>
<td>not tested</td>
<td>Highly reactive</td>
<td>MA</td>
</tr>
<tr>
<td>10</td>
<td><strong>2-methyl-2-propen-1-ol</strong></td>
<td>2-Methyl acrolein</td>
<td>not tested</td>
<td>Moderately reactive</td>
<td>MA, SBF</td>
</tr>
<tr>
<td>11</td>
<td><strong>2-methyl-2-buten-1-ol</strong></td>
<td>2-Methyl-2-butenal</td>
<td>12</td>
<td>Moderately reactive</td>
<td>MA, SBF</td>
</tr>
<tr>
<td>12</td>
<td><strong>2-methyl-2-penten-1-ol</strong></td>
<td>2-Methyl-2-pentenal</td>
<td>21</td>
<td>Moderately reactive</td>
<td>MA, SBF</td>
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<td>13</td>
<td><strong>3-methyl-2-buten-1-ol</strong></td>
<td>3-Methyl-2-butenal</td>
<td>13</td>
<td>Moderately reactive</td>
<td>SBF no MA</td>
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<td>14</td>
<td><strong>3-methyl-3-penten-2-ol</strong></td>
<td>3-Methyl-3-penten-2-one</td>
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<td>Highly reactive</td>
<td>MA</td>
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<td>15</td>
<td><strong>4-methyl-3-penten-2-ol</strong></td>
<td>4-Methyl-3-penten-2-one</td>
<td>26</td>
<td>Highly reactive</td>
<td>No alert</td>
</tr>
</tbody>
</table>

\(^1\) in mmol/l; \(^2\) OECD QSAR Toolbox; \(^3\) MA: Michael addition, SBF: Schiff base formers;
RAAF V: Mechanism of Reactivity and Trends in Effect Potency

Clustering of Effects / Order of Reactivity (C.4)/ Quantitative Aspects of Mechanism and Strength of Effects (4.3) / Source is Worst Case (C.6)

Clustering of potency of effects according to chemical reactivity

• Strengthen use of 2-propen-1-ol as source substance
• → How to prove a worst case?
• → suitability of *in chemico* assay for quantitative ranking (variability; relevance)?
• → confirm subcategory reactivity trends with testing of more (different) substances
Clustering of potency of effects according to chemical reactivity

- Strengthen use of 2-propan-1-ol as source substance
- How to prove a worst case?
- Suitability of in chemico assay for quantitative ranking (variability; relevance)?
- Confirm subcategory reactivity trends with testing of more (different) substances

Reactivity trend mostly relying on existing NAM in chemico data of reactivity potency clustering, supported by in silico and SEURAT-1 in vitro NAM
## βOA Case Study Considered with the RAAF

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<tr>
<th>AE</th>
<th>Remaining questions</th>
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<td>C.5</td>
<td>Reliability/adequacy source study(ies)</td>
</tr>
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</table>

### 4.1 Compounds the organism is exposed to, transformation

| 4 5 | ex vivo/in silico: metabolites→toxicants, not tertiary alcohols; also by hepatic organoids | • more (quant.) information: rate/speed of metabolism |

### 4.2 Common mechanism, qualitative aspects

| 4 5 | in chemico/in silico/in vitro data strengthen mechanism evidence, HSC activation markers the MoA to fibrosis |

### 4.3 Common mechanism, quantitative aspects

| 3 4 | in chemico data: only quant. info. on potency differences supported by in silico/in vitro | • Strengthen proof that source substance is the worst-case |

### 4.4 Exposure to other compounds

| 4 4 | • More details (quant.) kinetics: residual parent/further metabolites & effects |

### 4.5 Occurrence of other effects

| 4 4 | • Rule out other effects / metabolic mechanisms |

### C.6 Bias influencing prediction

| 4 4 | • Read-across valid for other structural variation members? |
## The beta OA Case Study: AO’s and NAM

<table>
<thead>
<tr>
<th>AE</th>
<th>AO w/o NAM</th>
<th>AO with NAM</th>
<th>NAM added info</th>
<th>Remaining questions</th>
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<tr>
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<td>3</td>
<td>• More details on study design and quality</td>
</tr>
</tbody>
</table>

### Overall AO’s ≥ 3

### Confidence increased by existing and SEURAT-1 NAM results

- **Compounds the organism is exposed to, transformation**
  - *ex vivo* in silico: metabolites: another moieties, not tertiary alcohols; not by the same acids
  - *in chemico* in silico/in vitro data strengthen *mechanism evidence*, HSC activation markers the **MoA to fibrosis**

- **Common mechanism, qualitative aspects**
  - *in chemico* data: only *quant. info. on potency differences* supported by *in silico/in vitro*

- **Exposure to other compounds**
  - More details (quant.) kinetics: residual parent/further metabolites & effects

- **Occurrence of other effects**
  - Rule out other effects / metabolic mechanisms

- **Bias influencing prediction**
  - Read-across valid for other structural variation members?
Information Added and Uncertainties Reduced by NAM

• **Metabolism of βOAs to toxicant**, reactivity of metabolites as opposed to parent compounds, link with structure (ex vivo perfused liver, *in silico, in chemico*)

• *in chemico* data: only quantitative data available to show **clustering of reactivity potency** (supported by *in silico/in vitro*)

• **Mechanism of adverse effect evidence strengthened** by *in chemico/in silico/ SEURAT-1 in vitro* data

• in particular: HSC activation markers in hepatic organoids confirm MoA **hypothesis of metabolic-mediated fibrosis**
Major Uncertainties

• Complexity of structures
  → Similarity / category boundaries and members
• Details on study design / quality of in vivo data, choice of NOAEL
• Potency of effects, order of reactivity
  → Proving the worst case for source compound
• Transformation mechanism (other than via ADH) / rates?
  → Reactivity potency vs kinetics
• Variation of metabolic pathways (aldehydes/ketones)
  → Possible other effects via further metabolites present (kinetics of transformations)
• Toxic reactivity mechanism? Map on AOP?
Possible further elucidation by NAM

- Complexity of structures → Similarity / category boundaries and members
- Details on study design / quality of in vivo data, choice of NOAEL
- Potency of effects, order of reactivity → Proving the worst case for source compound
- Transformation mechanism (other than via ADH) / rates?
  → Reactivity potency vs kinetics
- Variation of metabolic pathways (aldehydes/ketones)
  → Possible other effects via further metabolites present (kinetics of transformations)
- Toxic reactivity mechanism? Map on AOP?

Test more substances in the GSH reactivity in chemico assay

Any other activation of transformation than by ADH? → omics?

Generally: omics assays for metabolism pathways?
Conclusions

• βOA case study especially features
  - High structural complexity
  - Mechanistic aspects related to structures important for considered effect

• RAAF guides systematically through checking of all important points being covered and documented in sufficient detail for regulatory assessment, highlights kinetics issues

• NAM help in reducing uncertainties in particular related to mechanism

• Uncertainties remaining
  - in particular more (quantitative) kinetics/metabolism pathway data needed as highlighted by RAAF

• → more targeted NAM testing?
Stay in touch

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