Implementation of RAAF templates in Toolbox prediction report

Laboratory of Mathematical Chemistry
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2019
Outlook

• Aim
• What is RAAF and how does it works?
• RAAF Implementation in Toolbox
• Examples
Aim

To provide RAAF assessment elements in the prediction report
Outlook

• Aim
• What is RAAF and how does it works?
• RAAF Implementation in Toolbox
• Examples
What is RAAF?

• It has been developed by ECHA as internal tool providing a framework for a consistent and structured assessment of grouping and read across approaches under REACH

• The outcome of the assessment is a conclusion on whether the read across is scientifically acceptable or not

• The RAAF defines different scenarios for different read-across approaches

• Each scenario is associated with particular aspects (assessment elements, AEs) that are deemed crucial to the assessment
What is most important for the Read across assessment?

1. Distinguish whether it is analogue or category approach

2. To identify the basis of the read across hypothesis
   a. (Bio)transformation to common compound(s) – the read across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed
   b. Different compounds have the same type of effect(s) – the read across hypothesis is that the organism is not exposed to common compounds but rather, as a result of similarity, that different compounds have similar (eco)toxicological and fate properties. These compounds may be the source and target substances themselves or one or more of their (bio)transformation products.

3. For a category approach there is a need to take further account whether or not quantitative variations in the properties are observed among the category members

Total six scenarios are available: two for analogue approach and four for category approach
## RAAF scenarios

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>APPROACH</th>
<th>READ-ACROSS HYPOTHESIS BASED ON</th>
<th>QUANTITATIVE VARIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Analogue</td>
<td>(Bio)transformation to common compound(s)</td>
<td>Property of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.</td>
</tr>
<tr>
<td>2</td>
<td>Analogue</td>
<td>Different compounds have qualitatively similar properties</td>
<td>Properties of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.</td>
</tr>
<tr>
<td>3</td>
<td>Category</td>
<td>(Bio)transformation to common compound(s)</td>
<td>Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.</td>
</tr>
<tr>
<td>4</td>
<td>Category</td>
<td>Different compounds have qualitatively similar properties</td>
<td>Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.</td>
</tr>
<tr>
<td>5</td>
<td>Category</td>
<td>(Bio)transformation to common compound(s)</td>
<td>No relevant variations in properties observed among source substances and the same strength predicted for the target substance.</td>
</tr>
<tr>
<td>6</td>
<td>Category</td>
<td>Different compounds have qualitatively similar properties</td>
<td>No relevant variations in properties observed among source substances and the same strength predicted for the target substance</td>
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</tbody>
</table>
RAAF scenarios

[Diagram showing decision-making process for RAAF scenarios]
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RAAF Implementation in Toolbox

- The RAAF assessment elements (AEs) are added as part of the prediction report
- The information collected for the category elements (CEs) of Toolbox is used to fill in the AEs of RAAF
Schematic illustration of the exchange between the Toolbox CEs and the corresponding AEs from RAAF scenario
RAAF Implementation in Toolbox

Redesigning of the Toolbox report

- Prediction report is redesigned allowing specific information items to be added/removed to/from predefined places
- This is possible through a new data storage for reporting called “Report basket”
- The “Report basket” could be used for adding specific information items related to AE of the RAAF or for customization of the default report
- The content of the “Report basket” is presented further in this presentation
RAAF Implementation in Toolbox

• RAAF assessment elements are part of the Prediction report
RAAF Implementation in Toolbox

- RAAF assessment elements are part of the Prediction report
- Once “Add RAAF scenario” is selected, a specific Scenario (1 to 6) needs to be chosen from the menu
RAAF Implementation in Toolbox

- RAAF assessment elements are part of the Prediction report
- Once “Add RAAF scenario” is selected, a specific Scenario (1 to 6) needs to be chosen
- The AEs related to each scenario have been associated to corresponding report section

The report sections, where the AE appeared, are highlighted
RAAF Implementation in Toolbox

• RAAF assessment elements are part of the Prediction report
• Once “Add RAAF scenario” is selected, a specific Scenario (1 to 6) needs to be chosen
• The AEs related to each scenario have been associated to corresponding report section

A hint showing the purpose of each AE is provided to guide and help the user what needs to be added here.
RAAF Implementation in Toolbox

- RAAF assessment elements are part of the Prediction report
- Once “Add RAAF scenario” is selected, a specific Scenario (1 to 6) needs to be chosen
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Report basket with items that could be added to the RAAF assessment elements

The selected information appears in the report
RAAF Implementation in Toolbox

- RAAF assessment elements are part of the Prediction report
- Once “Add RAAF scenario” is selected, a specific Scenario (1 to 6) needs to be chosen
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New items with external content could be also added in the Report Basket
RAAF Implementation in Toolbox

- RAAF assessment elements are part of the Prediction report
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The image could be added in two ways:
- Browsing for the folder where the image was saved in advance
- Paste copied image
RAAF Implementation in Toolbox

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- Browsing for the folder where the image was saved in advance in *.jpg format
- Paste copied imagine
Outlook

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Analogue or Category approach is decided based on number (N) of analogues as follows:

- \( N \) of analogues \( \leq 3 \) is Analogue approach
- \( N \) of analogues > 3 is Category approach;
**RAAF Implementation in Toolbox**

**Example I:** Read across prediction for Skin sensitization according to **Scenario 2**

Example for a *Common underlying mechanism for metabolites of source and target substances* [1]

<table>
<thead>
<tr>
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<th>APPROACH</th>
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<tr>
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<td>Category</td>
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</tr>
<tr>
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<td>Category</td>
<td>Different compounds have qualitatively similar properties</td>
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<tr>
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<td>Category</td>
<td>(Bio)transformation to common compound(s)</td>
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<td>Different compounds have qualitatively similar properties</td>
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1. Read- Across Assessment Framework (RAAF), Appendix B: Scenario 2
Example I: Read across prediction for Skin sensitization according to Scenario 2

Example for a Common underlying mechanism for metabolites of source and target substances [1]

• The target is defined – CAS 56-18-8
Example I: Read across prediction for Skin sensitization according to Scenario 2

Example for a Common underlying mechanism for metabolites of source and target substances [1]

- The target is defined – CAS 56-18-8
- The target endpoint is: Skin Sensitisation / In Vivo / LLNA / EC3
Example I: Read across prediction for Skin sensitization according to Scenario 2

Example for a **Common underlying mechanism for metabolites of source and target substances** [1]

- The target is defined – CAS 56-18-8
- The target endpoint is: **Skin Sensitisation / In Vivo / LLNA / EC3**
- Primary group is defined accounting for *Skin metabolism simulator* and based on *Protein binding alerts for Skin sensitisation by OASIS profiler*
RAAF Implementation in Toolbox

Example 1: Read across prediction for Skin sensitization according to Scenario 2

Example for a Common underlying mechanism for metabolites of source and target substances [1]

- The target is defined – CAS 56-18-8
- The target endpoint is: Skin Sensitisation / In Vivo / LLNA / EC3
- Primary group is defined accounting for Skin metabolism simulator and based on Protein binding alerts for Skin sensitisation by OASIS profiler
- Alert performance for individual alerts obtained as a result of the metabolic activation

<table>
<thead>
<tr>
<th>#</th>
<th>Alert name</th>
<th>Alert performance*, %</th>
<th>Number of chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>Aldehydes</td>
<td>49.13</td>
<td>50.87</td>
</tr>
<tr>
<td>2</td>
<td>Bis aldehydes</td>
<td>82.35</td>
<td>17.65</td>
</tr>
<tr>
<td>3</td>
<td>Aldehydes &amp; Bis aldehydes</td>
<td>78.57</td>
<td>21.43</td>
</tr>
</tbody>
</table>

The primary group is defined based on the alert with highest performance: Bis aldehydes

1. Read- Across Assessment Framework (RAAF), Appendix B: Scenario 2
**Example I:** Read across prediction for Skin sensitization according to **Scenario 2**

**Example for a Common underlying mechanism for metabolites of source and target substances [1]**

- Analogue approach is applied (Number of analogues is 3)
- Target and analogues are activated as a result of skin metabolism by generating “Bis aldehyde”
- In this respect, they all have common reactivity pattern of generated skin metabolites
Example I: Read across prediction for Skin sensitization according to Scenario 2

Example for a Common underlying mechanism for metabolites of source and target substances [1]
Example I: Read across prediction for Skin sensitization according to **Scenario 2**

**Common underlying mechanism for metabolites of source and target substances** [1]

- Before Accepting the prediction in DGF one should come back to the *Category definition* and apply (by “OK” button) the Category elements related to Category consistency assessment.
- All selected Category elements are generated and automatically stored in the “Report basket”*
- Alert performance should be calculated before defining the primary group.

*Separate presentation on Category consistency and elements is available: “Category consistency report.pptx”*
RAAF Implementation in Toolbox

**Example I:** Read across prediction for Skin sensitization according to **Scenario 2**

Results in the report based on the items in the Basket
RAAF Implementation in Toolbox

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Results in the report based on the items in the Basket

1. Read- Across Assessment Framework (RAAF), Appendix B: Scenario 2
RAAF Implementation in Toolbox

**Example 1:** Read across prediction for Skin sensitization according to **Scenario 2**

**Results in the report based on the items in the Basket**

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**Table summarizing number of metabolites including parent with specific alerts**

<table>
<thead>
<tr>
<th>Protein binding alerts for skin sensitization by OASIS</th>
<th>P1 56-18-8</th>
<th>P2 109-55-7</th>
<th>P3 107-15-3</th>
<th>P4 111-40-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehydes</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bis aldehydes</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No alert found</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

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**CAS 56-18-8**

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Example I: Read across prediction for Skin sensitization according to Scenario 2

Results in the report based on the items in the Basket
### RAAF Implementation in Toolbox

**Example I:** Read across prediction for Skin sensitization according to **Scenario 2**

Results in the report based on the manually added item for Alert performance in the Basket

<table>
<thead>
<tr>
<th>#</th>
<th>Alert name</th>
<th>Alert performance, %</th>
<th>Number of chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Using of &quot;Skin metabolism simulator&quot; Combined parent and products requirements: No alert found &lt;AND&gt; Aldehydes &lt;AND&gt; Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)</td>
<td>78.57 21.43 11 3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Using of &quot;Skin metabolism simulator&quot; Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)</td>
<td>45.31 54.69 575 694</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Using of &quot;Skin metabolism simulator&quot; Combined parent and products requirements: Aldehydes (Protein binding alerts for skin sensitization by OASIS)</td>
<td>49.13 50.87 170 176</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Using of &quot;Skin metabolism simulator&quot; Combined parent and products requirements: Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)</td>
<td>82.35 17.65 14 3</td>
<td></td>
</tr>
</tbody>
</table>
RAAF Implementation in Toolbox

**Example I:** Read across prediction for Skin sensitization according to **Scenario 2**

Results in the report based on the manually added item with external content in the Basket.

1. Read Across Assessment Framework (RAAF), Appendix B: Scenario 2
**Example II:** Read across prediction for Repeated dose toxicity according to **Scenario 1**

Example for Identification of common (bio)transformation product [1]

The source substance A and the target substance B are structurally similar substances, which are rapidly and extensively absorbed after administration. Substance A is not (bio)transformed. Substance B is rapidly and extensively (bio)transformed to substance A, and therefore no/negligible systemic exposure to substance B occurs. The source substance A is the common compound in this analogue approach. The common compound A is solely responsible for the (absence of) effects. The effects of the target substance B are predicted to be equal to the effects of the source substance A for the property under consideration.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>PARENT SUBSTANCES</th>
<th>(BIO)TRANSFORMATION</th>
<th>COMMON COMPOUNDS</th>
<th>NON-COMMON COMPOUNDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A (\rightarrow) not transformed</td>
<td>A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>B (\rightarrow) A</td>
<td>A</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

Example for Identification of common (bio)transformation product [1]

- The target is defined – CAS 140-26-1
- The target multiplicities applying the following simulator: **Hydrolysis simulator (acidic)**

As a result of multiplication lists with parent and two child appear on Data matrix

1. Read Across Assessment Framework (RAAF), Section 4.4.2.2
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

Example for Identification of common (bio)transformation product [1]

- The target is defined – CAS 140-26-1
- The target multiplicities applying the following simulator: Hydrolysis simulator (acidic)
- The target endpoint is: Repeated Dose Toxicity / Rat / NOAEL

1. Read- Across Assessment Framework (RAAF), Section 4.4.2.2
**Example II:** Read across prediction for Repeated dose toxicity according to **Scenario 1**

**Example for Identification of common (bio)transformation product [1]**

- The target is defined – CAS 140-26-1
- The target multiplicities applying the following simulator: Hydrolysis simulator (acidic)
- The target endpoint is: Repeated Dose Toxicity / Rat / NOAEL
- Experimental data have been searched in the relevant TB databases for: Parent and its hydrolysis products

NOAEL data has been found for one of the hydrolysis products

1. Read- Across Assessment Framework (RAAF), Section 4.4.2.2
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

Example for Identification of common (bio)transformation product [1]

- The target is defined – CAS 140-26-1
- The target multiplicities applying the following simulator: Hydrolysis simulator (acidic)
- The target endpoint is: Repeated Dose Toxicity / Rat / NOAEL
- Experimental data have been searched in the relevant TB databases for: Parent and its hydrolysis products
- The NOAEL data found for one of the hydrolysis products is transferred to the parent chemical (based on the referenced document mentioned on slide 42) assuming it is obtained as a result of read across approach

1. Read- Across Assessment Framework (RAAF), Section 4.4.2.2
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

Example for Identification of common (bio)transformation product [1]

RAAF Scenario 1 is chosen for the Reporting and the associated Assessment elements (AEs) automatically appear in the following report sections:

- Category definition and members
- Consistency check

The sections containing AEs will be highlighted.

Information regarding different AEs should be provided by the user.
Example II: Read across prediction for Repeated dose toxicity according to **Scenario 1**

Example for Identification of common (bio)transformation product [1]

Information addressed to Scenario 1 – AE 1.1: Formation of common (identical) compound(s)

- Source substance B and Target substance A
- A is claimed to be metabolized to B and that the organism is only systemically exposed to B upon external exposure to A
- Therefore it is expected B to be responsible for the toxic effect
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

Example for Identification of common (bio)transformation product [1]

Information addressed to Scenario 1 – AE 1.1: Formation of common (identical) compound(s)

Manually editable field appears when click on “OK” and text could be added. Analogically, Image could also be added.
Example II: Read across prediction for Repeated dose toxicity according to Scenario 1

The information regarding AEs is available in the Prediction report (if provided by the user)

1.3. Profiles/Metabolisms

List of profiles/metabolisms

AE 1.1: Formation of common (identical) compound(s)

- AE 1.1. (text provided by user)
  - Source substance B and Target substance A.
  - A is claimed to be metabolized to B and that the organism is only systemically exposed to B upon external exposure to A.
  - Therefore it is expected B to be responsible for the toxic effect

AE 1.2: The biological targets for the common compound(s)

Not provided by user

AE 1.4: The impact of parent compounds

Not provided by user

AE 1.5: Formation and impact of non-common compounds

Not provided by user

Additional materials related to RAAF reporting are available at Toolbox website: https://qsartoolbox.org/support/#manuals

List with tutorials:
• An example illustrating RAAF Scenario 1 and related assessment elements
• An example illustrating RAAF Scenario 2 and related assessment elements
• An example illustrating RAAF Scenario 3 and related assessment elements
• An example illustrating RAAF Scenario 4 and related assessment elements
• An example illustrating RAAF Scenario 5 and related assessment elements
• An example illustrating RAAF Scenario 6 and related assessment elements