Assessment Workflows for Read Across and Substance Category Formation
Overview

• General aspects on non-testing approaches
• Guidance elements of the analogue approach / category formation workflow
• Practical example from the past
• AMBIT elements of the analogue approach / category formation workflow
General aspects on non-testing approaches

• General aspects on non-testing approaches

• Guidance elements of the analogue approach / category formation workflow

• Practical example from the past

• AMBIT elements of the analogue approach / category formation workflow
General aspects on non-testing approaches

**REACH**

**Article 13**

1. Information on intrinsic properties of substances may be generated by means other than tests, ...

   ... toxicity, information shall be generated whenever possible by means other than vertebrate animal tests ...

   ... alternative methods, for example ...

   ... from information from structurally related substances (grouping or read-across).

**Article 25**

1. In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort.
General aspects on non-testing approaches

Options that registrants use to cover REACH information requirements for different data endpoints

Extract from “The use of alternatives to testing on animals for the REACH Regulation” Third Report under Article 117(3) of the REACH Regulation
Guidance elements of the analogue approach / category formation workflow

• General aspects on non-testing approaches

• **Guidance elements of the analogue approach / category formation workflow**

• Practical example from the past

• AMBIT elements of the analogue approach / category formation workflow
Guidance elements of the analogue approach / category formation workflow

an analogue approach

START

Step 1: Identify potential analogues

Step 2: Data gathering for the analogues

Step 3: Evaluation of available data for adequacy

Search for additional analogues

Step 4: Construct a matrix of data availability

Not adequate

Obtain data point by testing

Step 5: Assess the adequacy of read-across and fill data gap

Adequate

Step 6: Document the read-across

STOP

category development

START

Step 0: Check whether the chemical is a member of a suitable category that has already been defined

YES, but new data are available

YES

STOP

NO

Step 1: Develop category by producing and defining and identify individual members of the category

Step 2: Gather data for each category member

Step 3: Evaluate available data for adequacy

Step 4: Construct a matrix of data availability

Not adequate

Step 6: Prepare and perform testing

Step 5: Perform a preliminary evaluation of the category and its data gaps

Step 7: Perform further assessment of the category

Adequate

Step 8: Document the finalized category and its rationale

STOP

Not adequate

Category approach may not be feasible

Revise category by adding and/or removing members and/or analogues

Extract from Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals
Guidance elements of the analogue approach / category formation workflow

**Analogue Approach**

- **Step 1**: Identify potential analogue(s)
  - **Task**: Identify potential analogue(s)
  - **Workload**: High
  - **Ambit Support**: High

- **Step 2**: Data gathering for the analogues
  - **Task**: Data gathering for the analogues
  - **Workload**: High
  - **Ambit Support**: High

- **Step 3**: Evaluation if available data are adequate
  - **Task**: Evaluation if available data are adequate
  - **Workload**: High
  - **Ambit Support**: Low

- **Step 4**: Construct a matrix of data availability
  - **Task**: Construct a matrix of data availability
  - **Workload**: High
  - **Ambit Support**: High

- **Step 5**: Assess the suitability of read-across, and fill data gaps
  - **Task**: Assess the suitability of read-across, and fill data gaps
  - **Workload**: High
  - **Ambit Support**: Mid

- **Step 6**: Document the read-across
  - **Task**: Document the read-across
  - **Workload**: Mid
  - **Ambit Support**: Mid

---

*Extract from Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals*
Practical example from the past

- General aspects on non-testing approaches
- Guidance elements of the analogue approach / category formation workflow
- Practical example from the past
- AMBIT elements of the analogue approach / category formation workflow
Practical example from the past

Data matrix for mammalian toxicity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tr>
<td>CAS No.</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
<td>12244-20-1</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
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<tr>
<td>Eye irritation</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
<td>Not irritating</td>
</tr>
<tr>
<td>Skin sensitization</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
<td>Not sensitising</td>
</tr>
<tr>
<td>Skin sensitization</td>
<td>Not sensitising</td>
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<td>Skin sensitization</td>
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<td>Not sensitising</td>
<td>Not sensitising</td>
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<td>Not sensitising</td>
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<td>Not sensitising</td>
</tr>
</tbody>
</table>

Naphtol AS Pigment
Category

Pigment Red XY

Not skin sensitising

Skin sensitization
### Practical example from the past

**Data matrix for mammalian toxicity**

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>Category</th>
<th>Mammalian</th>
<th>Cytotoxicity</th>
<th>Reproductive</th>
<th>Developmental</th>
<th>Embryotoxicity</th>
<th>Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphtol AS Pigment</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Number of fields to be filled for mammalian toxicity**

- 16 category members
- 17 endpoints
- Total: 272 fields

**Additional fields have to be filled for:**
- physicochemical properties
- environmental fate
- environmental toxicity
AMBIT elements of the analogue approach workflow

• General aspects on non-testing approaches

• Guidance elements of the analogue approach / category formation workflow

• Practical example from the past

• AMBIT elements of the analogue approach / category formation workflow
AMBIT elements of the analogue approach /category formation workflow

Workflow for read across and category formation

5 MAIN STEPS

7 SUB STEPS
AMBIT elements of the analogue approach workflow

- **Step 1: Identify potential analogue(s)**

### Assessment identifier

<table>
<thead>
<tr>
<th>Assessment title*</th>
<th>Glymes category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner*</td>
<td>Li Qiang</td>
</tr>
<tr>
<td>Purpose*</td>
<td>demonstration</td>
</tr>
<tr>
<td>Version</td>
<td>??</td>
</tr>
<tr>
<td>Version start date</td>
<td>??</td>
</tr>
<tr>
<td>Version last modified on</td>
<td>??</td>
</tr>
<tr>
<td>Status</td>
<td>??</td>
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<td>Assessment code*</td>
<td>GlyCat01</td>
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<td>Assessment Doclink(s)*</td>
<td>local</td>
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<td>??</td>
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<tr>
<td>Users with write access*</td>
<td>??</td>
</tr>
<tr>
<td>Users with read access*</td>
<td>??</td>
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</tbody>
</table>
AMBIT elements of the analogue approach workflow

- **Step 1: Identify potential analogue(s)**
AMBIT elements of the analogue approach workflow

• **Step 1: Identify potential analogue(s)**
AMBIT elements of the analogue approach workflow

- **Step 1: Identify potential analogue(s)**
AMBIT elements of the analogue approach workflow

- **Step 1: Identify potential analogue(s)**
### AMBIT elements of the analogue approach workflow

- **Step 1: Identify potential analogue(s)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>CasRN</th>
<th>EC number</th>
<th>Names</th>
<th>Similarity</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>111-96-6</td>
<td>203-924-4</td>
<td>bis(2-methoxyethyl) ether</td>
<td>Ethane, 1,1'-oxybis 2-methoxy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>111-77-3</td>
<td>203-906-6</td>
<td>2-(2-methoxyethoxy)ethanol</td>
<td>Ethanol, 2-(2-methoxyethoxy)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>112-35-6</td>
<td>203-962-1</td>
<td>2-(2-(2-methoxyethoxy)ethoxy)ethanol</td>
<td>Ethanol, 2-(2-methoxyethoxy)ethoxy</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>112-36-7</td>
<td>203-963-7</td>
<td>bis(2-ethoxyethyl) ether</td>
<td>Ethylene glycol diethyl ether</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>112-49-2</td>
<td>203-977-3</td>
<td>1,2-bis(2-methoxyethoxy)ethane</td>
<td>2,5,8,11-tetraoxadodecane</td>
<td>0.89</td>
</tr>
</tbody>
</table>
AMBIT elements of the analogue approach workflow

• **Step 1: Identify potential analogue(s)**
AMBIT elements of the analogue approach workflow

- **Step 2: Data gathering for analogues**

<table>
<thead>
<tr>
<th>Diagram</th>
<th>CasRN</th>
<th>EC number</th>
<th>Names</th>
<th>Rationale</th>
<th>Tag</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1 -</td>
<td>110-71-4</td>
<td>203-794-9</td>
<td>1,2-dimethoxyethane</td>
<td>Ethane, 1,2-dimethoxy-</td>
<td>same functional group, comparable metabolism</td>
</tr>
<tr>
<td>- 2 -</td>
<td>111-96-6</td>
<td>203-924-4</td>
<td>bis(2-methoxyethyl) ether</td>
<td>Ethane, 1,1'-oxybis 2-methoxy-</td>
<td>same functional group, comparable metabolism</td>
</tr>
<tr>
<td>- 3 -</td>
<td>112-49-2</td>
<td>203-977-3</td>
<td>1,2-bis(2-methoxyethoxy)ethane</td>
<td>2,5,8,11-tetraoxadecane</td>
<td>same functional group, comparable metabolism</td>
</tr>
<tr>
<td>- 4 -</td>
<td>143-24-8</td>
<td>205-594-7</td>
<td>bis(2-(2-methoxyethoxy)ethyl) ether</td>
<td>2,5,8,11,14-pentaoxaapentadecane</td>
<td>same functional group, comparable metabolism</td>
</tr>
</tbody>
</table>
AMBIT elements of the analogue approach workflow

- **Step 2: Data gathering for analogues**
AMBIT elements of the analogue approach / workflow

• **Step 3:** Evaluation of available data for adequacy
AMBIT elements of the analogue approach workflow

**Step 3: Evaluation of available data for adequacy**
**Step 4: Construct a matrix of data availability**

---

### Assessment details

<table>
<thead>
<tr>
<th>CasRN</th>
<th>Substance Name</th>
<th>ISUJJID</th>
<th>Data source</th>
<th>Tag</th>
<th>Diagram</th>
<th>7.2.1. Acute toxicity – oral</th>
<th>7.2.2. Acute toxicity – inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diolyme</td>
<td>IUCS-243</td>
<td>Clarient Produkte (Deutschland) GmbH / Sulzbach am Taunus / Germany</td>
<td>CH</td>
<td>LD50 = 4750 mg/kg bw (Species = rat)</td>
<td>LD50 = 11 mg/L air (Species = rat)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Triglyme</td>
<td>IUCS-203</td>
<td>Clarient Produkte (Deutschland) GmbH / Sulzbach am Taunus / Germany</td>
<td>CH</td>
<td>LD50 = 5389 mg/kg bw (Species = rat)</td>
<td>LD50 = 5877 mg/kg bw (Species = rat)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Tetruglyme</td>
<td>IUCS-234</td>
<td>Clarient Produkte (Deutschland) GmbH /</td>
<td>CH</td>
<td>LD50 = 3826 mg/kg bw (Species = rat)</td>
<td>LD50 = 11 mg/L air (Species = rat)</td>
<td></td>
</tr>
</tbody>
</table>
AMBIT elements of the analogue approach workflow

**Step 4:** Construct a matrix of data availability
**Step 5:** Assess the adequacy of read-across and fill data gap
AMBIT elements of the analogue approach workflow

**Step 4:** Construct a matrix of data availability
**Step 5:** Assess the adequacy of read-across and fill data gap
AMBIT elements of the analogue approach workflow

**Step 6: Document the read-across**

---

**Ambit Assessment Report**

**Glymes category Demo**

**Author:** Unknown  
**Date:** 28.04.2016  
**Assessment code:** 27e8c3ba-0017-4314-bd82-3d265a6e6ade  
**Purpose:** demonstration and testing

### 1. Assessment Identifiers

<table>
<thead>
<tr>
<th>Assessment title:</th>
<th>Glymes category Demo</th>
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<tbody>
<tr>
<td>Owner:</td>
<td>Unknown</td>
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<td>Purpose:</td>
<td>demonstration and testing</td>
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<td>Version:</td>
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<td>Status:</td>
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<td>27e8c3ba-0017-4314-bd82-3d265a6e6ade</td>
</tr>
</tbody>
</table>

The original assessment in Ambit can be found via **Assessment ID**
AMBIT elements of the analogue approach workflow

**Step 6: Document the read-across**

### 2. List of structures for assessment

In the assessment, similar structures were selected from exact structure, substructure and/or similarity searches, or were added manually. The rationale for the selection is given in the table.

<table>
<thead>
<tr>
<th>Diagram</th>
<th>CasRN</th>
<th>EC number</th>
<th>Names</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>110-71-4</td>
<td>203-794-9</td>
<td>1,2-dimethoxyethane</td>
<td>same functional group, comparable metabolism</td>
</tr>
<tr>
<td></td>
<td>111-96-6</td>
<td>203-924-4</td>
<td>bis(2-methoxyethyl) ether</td>
<td>same functional group, comparable metabolism</td>
</tr>
</tbody>
</table>

### 3. List of substances related to the structures

In the following, for each structure listed in chapter 2, substances were selected and the rationale is given.

<table>
<thead>
<tr>
<th>Diagram</th>
<th>CasRN</th>
<th>EC number</th>
<th>Names</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>110-71-4</td>
<td>203-794-9</td>
<td>1,2-dimethoxyethane</td>
<td>same functional group, comparable metabolism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>Substance Type</th>
<th>Public name</th>
<th>Reference substance</th>
<th>Owner</th>
<th>Info</th>
<th>Contains in as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glymes Ethylene glycol dimethyl ether (GDMME)</td>
<td>Monoester</td>
<td>Monoglyme</td>
<td>Monoglyme</td>
<td>Clariant Produkte (Deutschland) GmbH &amp; Co. KG (Taunus, Germany)</td>
<td>constituents</td>
<td></td>
</tr>
</tbody>
</table>
AMBIT elements of the analogue approach workflow

**Step 6: Document the read-across**

4. Substance composition matrix

In the following, for each substance, the associated structure(s) and the composition are given.

<table>
<thead>
<tr>
<th>CAS</th>
<th>Substance Name</th>
<th>ISURID</th>
<th>Data source</th>
<th>Tag</th>
<th>Diagram</th>
<th>Constituent Name</th>
<th>Content</th>
<th>Contained As</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diglyme</td>
<td>IUCS:438545b-3c6c-493c-836c-5cd2756c776c</td>
<td>Clariant Produkte (Deutschland) GmbH / Sulzbach am Taunus / Germany</td>
<td>CH4</td>
<td></td>
<td>Ethene, 1,1'-oxygen[2-methoxy-]</td>
<td>ca. 92 % (w/w)</td>
<td>constituent</td>
</tr>
<tr>
<td>2</td>
<td>Tetragnlyme</td>
<td>IUCS:541c0a6-0033-45ee:8136-40e478daeb0f4</td>
<td>Clariant Produkte (Deutschland) GmbH / Sulzbach am Taunus / Germany</td>
<td>CH4</td>
<td></td>
<td>2,5,8,11-Tetraoxadecane</td>
<td>2.4 % (w/w)</td>
<td>impurity</td>
</tr>
</tbody>
</table>

Inchi = 1S/C10H2005/c1-11-3-5-13-7-9-15-10-8-14-6-4-12-2/h3-10H2,1-2H3 > 99 % (w/w) constituent
### AMBIT elements of the analogue approach workflow

#### Step 6: Document the read-across

### 5. Assessment data matrix

In the following, for each substance, the associated endpoint data are given, either experimental data, waiving or read-across.

For detailed data or rationale for waiving and read-across, click hyperlinks in the table. These data or rationales can also be found in the annex of the report.

<table>
<thead>
<tr>
<th>Tag</th>
<th>CH-CH</th>
<th>CH-CH-CH</th>
<th>CH-CH-CH-CH</th>
<th>CH-CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance name</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAS No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.7. Partition coefficient</td>
<td>0.36 (Temperature = 25.0 °C, pH = 7.0)</td>
<td>0.84 (Temperature = 23.0 °C, pH = ca. 7.0 ca.)</td>
<td>0.52 (Temperature = 23.0 °C, pH = 7.4)</td>
<td></td>
</tr>
<tr>
<td>7.2.1. Acute toxicity - oral</td>
<td>LD50 = 4760 mg/kg bw (Species = rat)</td>
<td>LD50 = 3850 mg/kg bw (Species = rat)</td>
<td>LD50 = 3850 mg/kg bw/day</td>
<td>LD50 = 5390 mg/kg bw (Species = rat)</td>
</tr>
<tr>
<td>7.2.2. Acute toxicity - inhalation</td>
<td>LC50 = 11 mg/L (Species = rat)</td>
<td></td>
<td>LC50 = 11 mg/m³ (Species = rat)</td>
<td>100 &gt; 6900 mg/kg bw (Species = rat)</td>
</tr>
<tr>
<td>7.2.3. Acute toxicity - dermal</td>
<td>erythema score = 0.5</td>
<td>edema score = 0.5</td>
<td>erythema score = 0.5</td>
<td>edema score = 0.5</td>
</tr>
<tr>
<td>7.3.1. Skin irritation / Corrosion</td>
<td></td>
<td></td>
<td></td>
<td>overall irritation score = 0</td>
</tr>
<tr>
<td>7.3.2. Skin sensitization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.3.3. Skin irritation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7.3.4. Skin Irritation / Corrosion</td>
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<tr>
<td>7.3.5. Skin Sensitization</td>
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<td></td>
<td></td>
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</tbody>
</table>
AMBIT elements of the analogue approach workflow

**Step 6: Document the read-across**

- Create assessment report
- Create Excel file with all used experimental data
- Create Excel file with the initial matrix
- Create Excel file with the working matrix
CONCLUSION

In contrast to the traditional procedure for analogue approach and category formation, AMBIT enables the assessor to generate

- more consistent,
- high-quality reports,
- involving less efforts and
- spending less time.
Thank you for your attention!

so does anyone have any questions?

@hugh
Backup
Guidance elements of the analogue approach / category formation workflow

**Analogue Approach**

1. Identify potential analogues
2. Data gathering for the analogues
3. Evaluation of available data for adequacy
4. Construct a matrix of data availability
5. Assess the adequacy of read-across and fill data gap
6. Document the read-across

**Category Development**

1. Check whether the chemical is a member of a suitable category that has already been defined
2. Develop category by producing and defining and identifying individual members of the category
3. Gather data for each category member
4. Evaluate available data for adequacy
5. Construct a matrix of data availability
6. Prepare and perform testing
7. Perform a preliminary evaluation of the category and its data
8. Document the finalized category and its rationale
9. Category approach may not be feasible

Extract from Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals
AMBIT elements of the analogue approach workflow

- **Step 1:** Identify potential analogue(s)

Search structures and associated data

Search IUCLID substances by identifiers

Search IUCLID substances by endpoint data
AMBIT elements of the analogue approach workflow

- **Step 1:** Identify potential analogue(s)
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