

OECD QSAR Toolbox v.4.2

An example illustrating RAAF Scenario 2 and related assessment elements

Outlook

- **Background**
- Objectives
- Specific Aims
- Read Across Assessment Framework (RAAF)
- The exercise
- Workflow

Background

- This is a step-by-step presentation designed to take the Toolbox user through the workflow of a data gap filling exercise and justification of the outcome.
- The read-across prediction will be justified by fulfilling all information requirements according to the Read Across Assessment Framework (RAAF).

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Objectives

This presentation demonstrates a number of functionalities of the Toolbox:

- Define target endpoint;
- Calculation of alert performance (AP) accounting for metabolism;
- Searching of analogues accounting for metabolism;
- Category consistency check;
- Selection of RAAF scenario;
- Filling in the report sections related to each read-across assessment element.

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Specific Aims

- To familiarize the user with the Read-Across Assessment Framework (RAAF) and more specifically with Scenario 2;
- To introduce to the user the read across assessment elements;
- To introduce to the user the report basket;
- To provide sufficient information allowing a scientific assessment of the outcome;
- To explain to the Toolbox user the rationale behind each step of the exercise.

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- **Read-Across Assessment Framework (RAAF)**
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Read-Across Assessment Framework (RAAF) Overview

- RAAF was developed by ECHA as an internal tool which provides 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).
- Total six scenarios are available: two for analogue approach and four for category approach.

Read-Across Assessment Framework (RAAF)

Selection of a RAAF scenario

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

*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

Read-Across Assessment Framework (RAAF)

Selection of a RAAF scenario

- Distinguish whether it is an analogue or a category approach*
- To identify the basis of the read across hypothesis
 - (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
 - 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.
- 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

*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

Read-Across Assessment Framework (RAAF)

Selection of RAAF scenario

- Each scenario consists of a pre-defined set of assessment elements (AEs) that, when taken together, cover all of the essential scientific aspects that need to be addressed in the read-across approach for a particular scenario.*
- Each AE reflects a critical scientific aspect of a read-across.
- The AEs could be:
 - **common** for all scenario within one approach - common AEs for Scenario 1 and 2 (analogue approach) and common AEs for Scenario 3, 4, 5 and 6 (category approach)
 - **specific** – addressing specific scenario.

*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

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The Example

- In this example we will predict the skin sensitization potential of *1,3-Propanediamine, N-(3-aminopropyl)-* [CAS# 56-18-8], which will be the “target” chemical;
- The category will be defined by the mechanism of protein binding accounting for metabolism common to all the chemicals in the category;
- A read-across approach will be used for the prediction. The read-across will be based on analogue approach expressed as common underlying mechanism for metabolites of source and target substances;
- Read-across assessment elements will be included to the report;
- Examples for the possible content of each of AEs will be provided.

The Example

Sidebar On Skin Sensitization

- Allergic contact dermatitis that results from skin sensitization is a significant health concern.
- Skin sensitization is a toxicological endpoint that is complex and conceptually difficult.
- However, there is growing agreement that most organic chemicals must react covalently with skin proteins in order to behave as skin sensitizers.
- Therefore, mechanisms by which organic chemicals bind with proteins are relevant to grouping chemicals that may be skin sensitizing agents.

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Workflow

- **The Toolbox has six modules, which are used in a sequential workflow:**
 - Input
 - Profiling
 - Data
 - Category Definition
 - Data Gap Filling
 - Report

The modules will be presented in different sequence than the one showed above.

Input Overview

- This module provides the user with several means of entering the chemical of interest or the target chemical.
- Since all subsequent functions are based on chemical structure, the goal here is to make sure the molecular structure assigned to the target chemical is the correct one.

Input Screen

Input target chemical by CAS#

1

2

3

4

Search by CAS #

56188 Search

OK Cancel

Select All Unselect All Invert Selection Selected 1 of 1

1	CAS	56-18-8	
	SMILES	NCCCNCCCN	
	CS Relation	High	
<input checked="" type="checkbox"/>	Substance	Mono constituent	<chem>NCCCNCCCN</chem>
	Composition		
	Name	1,3-Propanediamine, N-(3-a... 1,3-Propanediamine, N1-(3-... 1,3-propanediamine, n-(3-a...	

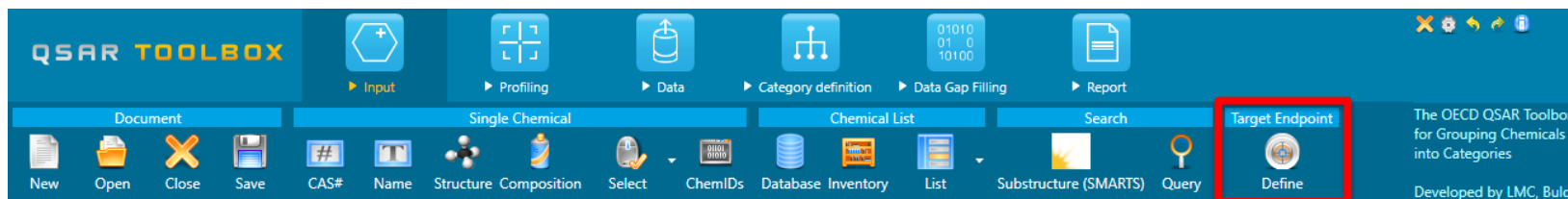
Click **CAS#** button (1); Type CAS **56-18-8** in the blank field (2) and click **Search** (3). When the structure appears, click **OK** (4).

Input

Define target endpoint

Defining of the endpoint allows entering the endpoint of interest e.g. EC3, LC50, gene mutation etc., along with specific metadata information. Based on the metadata, different relevancy scores for profiles could be provided for same endpoint.

Calculation of alert performance (AP) is only possible if the target endpoint is preliminary selected.



Input

Define target endpoint

By clicking **Define** (1) you could select the target endpoint. Select **Sensitisation** in the *Human health hazards* category (2) and click **Next** (3). Select **EC3** endpoint (4) from the drop-down menu and then consecutively the following metadata: **Assay: LLNA, Organ: Skin, Type of method: In Vivo** (5). Finally click on **Finish** (6).

Input

Define target endpoint

Once the endpoint is defined along with its metadata, they appear in the endpoint tree and the corresponding row of the data matrix is highlighted.

The screenshot displays the QSAR Toolbox software interface. The top menu bar includes options like 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. Below this, a secondary menu bar shows 'Document', 'Single Chemical', 'Chemical List', 'Search', and 'Target Endpoint'. The 'Target Endpoint' menu is active, showing options like 'New', 'Open', 'Close', 'Save', 'CAS#', 'Name', 'Structure', 'Composition', 'Select', 'ChemIDs', 'Database', 'Inventory', 'List', 'Substructure (SMARTS)', 'Query', and 'Define'. The main workspace is divided into two panes. The left pane, titled 'Documents', shows 'Document 1' with CAS# 56188. The right pane, titled 'Filter endpoint tree...', shows a hierarchical tree of endpoints. The 'Sensitisation' endpoint is selected, and its sub-entries 'Skin', 'in Vivo', and 'LLNA' are visible. The 'LLNA' entry is further expanded to show 'EC3'. The row corresponding to the selected endpoint in the data matrix is highlighted in yellow.

Data Overview

- “Data” refers to the electronic process of retrieving the environmental fate, ecotoxicity and toxicity data that are stored in the Toolbox.
- Data gathering can be executed in a global fashion (i.e., collecting all data for all endpoints) or on a more narrowly defined basis (e.g., collecting data for a single or limited number of endpoints).

Data Gather data

The screenshot shows the QSAR Toolbox software interface. The top toolbar has a 'Data' button highlighted with a red dashed box and labeled '1'. Below the toolbar, the 'Data' menu is open, and the 'Gather' option is highlighted with a red box and labeled '3'. In the 'Databases' section of the left sidebar, two databases are checked: 'REACH Skin sensitisation database (normalise)' and 'Skin Sensitization', with a callout '2' pointing to them. A central window titled 'Filter endpoint tree...' shows a tree structure with 'EC3' highlighted in yellow. A pop-up dialog box with a red border and labeled '4' contains the text '5 points added across 1 chemicals.' and an 'OK' button.

1. Go to **Data** module;
2. Select the highlighted databases (these are the databases containing data related to the defined endpoint);
3. Click **Gather**.
4. A pop-up message informs that there are 5 experimental data points for the target chemical.

Data

Gather data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s).
- It should be kept in mind that the search for data and analogues (and further calculation of AP) is performed only among the chemicals which are listed in the selected databases. In this example only the *Skin sensitization database* and *REACH Skin sensitization database (normalized)* are selected.
- In this example, a pop-up window appears stating there are 5 experimental data points for the target chemical. Positive experimental data are available.
- Go to the *Profiling* module to check for the possible reasons of the positive effect (to check for an alert identified in the target chemical).

Profiling

Overview

- “Profiling” refers to the electronic process of retrieving relevant information on the target compound, other than environmental fate, ecotoxicity and toxicity data, which are stored in the Toolbox database.
- Available information includes likely mechanism(s) of action, as well as observed or simulated metabolites.

Profiling

Profiling the target chemical

The screenshot displays the QSAR Toolbox interface. At the top, the 'Profiling' tab is active. The 'Apply' button is highlighted with a red box and a callout '2'. Below it, the 'Profiling methods' and 'Metabolism/Transformations' panels are visible. In both panels, the 'Suitable' category is selected, and several sub-methods are checked, marked with callout '1'. The 'Filter endpoint tree...' window on the right shows a list of hazard endpoints, with 'EC3' highlighted in yellow.

1. Select all *suitable* profiling schemes and simulators;
2. Click **Apply**

Profiling

Profiling results

- 1) No alerts are identified in the target structure as a parent;
- 2) No metabolites are produced as a result of abiotic activation (*Autoxidation simulator*);
- 3) 5 metabolites are produced as a result of biotic activation (*Skin metabolism simulator*);
- 4) Endpoint specific protein binding alerts are identified in the metabolites produced by the Skin metabolism simulator.

See on the next slide

Profiling

Profiling results

The screenshot shows the QSAR Toolbox interface. The top toolbar includes icons for Input, Profiling, Data, Category definition, Data Gap Filling, and Report. Below the toolbar are sections for Profiling and Custom profile. The main window displays a filter endpoint tree on the left and a results table on the right. The chemical structure shown is NCCNCCN. The results table shows various endpoints and their corresponding findings, with four red boxes and callouts (1, 2, 3, 4) highlighting specific results.

Endpoint	Result
General Mechanistic - Protein binding by OASIS	No alert found
Endpoint Specific - Protein binding alerts for skin sensitization according to GHS	No alert found
Endpoint Specific - Protein binding alerts for skin sensitization by OASIS	No alert found
Metabolism/Transformations - Autoxidation simulator	0 metabolite(s)
Metabolism/Transformations - Skin metabolism simulator	5 metabolite(s)
General Mechanistic - Protein binding by OASIS	1 x Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis...
Endpoint Specific - Protein binding alerts for skin sensitization according to GHS	1 x Skin sensitization Category 1A 1 x Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis... 2 x No alert found
Endpoint Specific - Protein binding alerts for skin sensitization by OASIS	2 x Schiff base formation >> Schiff base formation with carbonyl compounds >> Ald... 3 x Schiff base formation 3 x Schiff base formation >> Schiff base formation with carbonyl compounds

Recap

- In module one, you entered the target chemical and defined the target endpoint.
- In the *Data* module, you saw the database corresponding to the defined target endpoint. You also found some experimental data for the target available in the selected databases.
- In the *Profiling* module, you profiled the target chemical with profiling schemes and metabolic simulators, suitable for the selected target endpoint.
- Protein binding alerts for skin sensitization were identified for some of the metabolites produced by simulating of biotic activation.
- Click “Category Definition” to move to the next module.

Category Definition Overview

- This module provides the user with several means of grouping chemicals into a toxicologically meaningful category that includes the target molecule.
- This is the critical step in the workflow.
- Several options are available in the Toolbox to assist the user in refining the category definition.

Category Definition

Grouping methods

- The different grouping methods allow the user to group chemicals into chemical categories according to different measures of “similarity” so that within a category data gaps can be filled by read-across.
- For example, starting from a target chemical for which a specific protein binding mechanism is identified, analogues can be found which can bind by the same mechanism and for which experimental results are available.
- If no alert is identified in the target structure, but is identified in its metabolites, analogues can be searched accounting for metabolism. In this way the target chemical and the identified analogues will have similar metabolic pattern.
- When more than one alert is found in the target structure before or after metabolic activation, Alert performance could be used to define which of them is the most suitable for primary categorization.

Category Definition

Searching for analogues accounting for skin metabolism

1 Click **Define with metabolism**; **2**. Select *Skin metabolism simulator*; **3**. Click **OK**; **4**. Target and all metabolites produced by the selected simulator appear

Chemical	Query	Criteria
Parent	none	No criteria. 4
Metabolite 1	none	No criteria.
Metabolite 2	none	No criteria.
Metabolite 3	none	No criteria.
All chemicals		
Parent & Metabolites	none	No criteria.

Category Definition

Searching for analogues accounting for skin metabolism

The screenshot displays the 'Grouping options (Skin metabolism simulator)' dialog box. It features a table with the following structure:

Chemical	Query	Criteria
Parent	none	No criteria.
Metabolite 1	NH ₃	No criteria.
Metabolite 2	none	No criteria.
Metabolite 3		
All chemicals		
Parent & Metabolites	profile	Profiler: Protein binding alerts for skin sensitization by OASIS Options: Edit

The 'Target' window on the right shows a list of alerts and profiles. The 'Alerts' section includes: 'No alert found', 'Schiff base formation', 'Schiff base formation >> Schiff base formation with carbonyl compounds', 'Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes', and 'Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes'. The 'Profiles' section includes: '(N/A)', 'Acylation', 'Acylation >> (Thio)carbamylation of protein nucleophiles', 'Acylation >> (Thio)carbamylation of protein nucleophiles >> Isocyanates, Isothiocyanates', 'Acylation >> Acyl transfer via nucleophilic addition reaction', 'Acylation >> Acyl transfer via nucleophilic addition reaction >> Carbodiimides', and 'Acylation >> Direct acylation involving a leaving group'. The 'Combine profiles' section has radio buttons for 'AND' (selected) and 'OR', and checkboxes for 'Invert result' and 'Strict'.

1. Define *profile* query for the package – “Parent & Metabolites” and then select *Protein binding alerts for skin sensitization by OASIS*.
2. Click **Edit** to see all identified alerts in the parent and metabolites.

Category Definition

Alert performance calculation

The screenshot displays the 'Grouping options (Skin metabolism simulator)' dialog box. It features a table with columns 'Chemical', 'Query', and 'Criteria'. The 'Parent' row is highlighted in red and contains a chemical structure, 'none', and 'No criteria.'. The 'Metabolite 1' row is highlighted in black. An 'Aggregation options' sub-dialog is open, showing a list of scales with 'Skin sensitisation II (ECETOC)' selected. A 'Calculate' button is highlighted in the main dialog. Numbered callouts 1, 2, and 3 point to the 'Scales' button, the selected scale, and the 'Calculate' button respectively. A text box explains the steps: 'Click **Scales** button (1), select *Skin sensitization II (ECETOC)* scale (2) and then click **Calculate** (3) to evaluate the alert performance.'

Category Definition

Alert performance calculation

Using "Skin metabolism simulator" Combined parent and products requirements: Schiiff base formation >> Schiiff base formation with carbonyl compounds >> Aldehydes<AND>Schiiff base formation >> Schiiff base formation with carbonyl compounds >> Bis aldehydes<AND>No alert found (Protein binding alerts for skin sensitization by OASIS)	Positive Negative	78.57% 21.43%	Show chemicals... With data(11)... Show chemicals... With data(3)...	Show all(14)...
Using "Skin metabolism simulator" Combined parent and products requirements: Schiiff base formation >> Schiiff base formation with carbonyl compounds >> Aldehydes (Protein binding alerts for skin sensitization by OASIS)	Positive Negative	48.99% 51.01%	Show chemicals... With data(169)... Show chemicals... With data(176)...	Show all(345)...
Using "Skin metabolism simulator" Combined parent and products requirements: Schiiff base formation >> Schiiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	Positive Negative	82.35% 17.65%	Show chemicals... With data(14)... Show chemicals... With data(3)...	Show all(17)...
Using "Skin metabolism simulator" Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)	Positive Negative	45.35% 54.65%	Show chemicals... With data(575)... Show chemicals... With data(693)...	Show all(1268)...

Statistic for **all** alerts identified in the package "Parent & Metabolites"

Statistic for **each** of the alerts identified in the package "Parent & Metabolites"

The alert with the best performance in this case. "Bis aldehydes" alert will be used for searching for analogues.

! Keep in mind that the statistic is obtained from the chemicals and data, available in the selected databases

Category Definition

Searching for analogues accounting for skin metabolism

Grouping options (Skin metabolism simulator)

Chemical Query Criteria

Chemical	Query	Criteria
Parent	none	No criteria.
Metabolite 1	NH ₃	No criteria.
Metabolite 2		No criteria.
Metabolite 3		
All chemicals		
Parent & Metabolites	profile	Profiler: Protein binding alerts for skin sensitization by OASIS Options: Edit

Target: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes

Profiles (N/A)

- Acylation
- Acylation >> (Thio)carbamylation of protein nucleophiles
- Acylation >> (Thio)carbamylation of protein nucleophiles >> Isocyanates, Isothiocyanates
- Acylation >> Acyl transfer via nucleophilic addition reaction

Combine profiles: AND OR Invert result Strict

Click **Edit** (1) button and remove all alerts except this with the best performance (*Bis aldehydes*) (2). Confirm the change by clicking **OK** (3) and click **OK** (4) in the main window to start the search.

Category Definition

Summary information for Analogues

17 chemicals with 44 experimental results related to the defined target endpoint are found across all 29 analogues.

The screenshot shows the QSAR Toolbox interface with the 'Category definition' workflow active. The 'Filter endpoint tree' on the left is expanded to 'EC3', which is highlighted in yellow. A tooltip indicates that 17 out of 44 chemicals have 0.882% of the available experimental data. The main table displays chemical structures and their associated experimental data across various hazard categories.

Structure	1 [target]	2	3	4	5	6	7	8
Structure	<chem>CCCCCCCC</chem>	<chem>C1CCNCC1</chem>	<chem>C1=CC=CC=C1</chem>	<chem>C1=CC=C(C=C1)C</chem>	<chem>C1=CC=C(C=C1)C</chem>	<chem>C1=CC=C(C=C1)C</chem>	<chem>C1=CC=C(C=C1)C</chem>	<chem>C1=CC=C(C=C1)C</chem>
Human Health Hazards								
Acute Toxicity								
Bioaccumulation								
Carcinogenicity								
Developmental Toxicity / Teratogenicity								
Genetic Toxicity								
Immunotoxicity								
Irritation / Corrosion								
Neurotoxicity								
Photoinduced toxicity								
Repeated Dose Toxicity								
Sensitisation								
in Vivo								
GPMT	16/21	M: Category 1B	M: Positive	M: Negative		M: Negative		M: Category 1A
HRIPT	1/2							
LLNA								
EC3	17/44	M: 0.882 %			M: 1.68 %		M: Positive	M: Ne
Miscellaneous	6/57	M: Category C	M: Category B					

Chemical statistics presenting the number of chemicals and the available experimental data.

Data Gap Filling Overview

- “Data Gap Filling” module give access to five different data gap filling tools:
 - Read-across
 - Trend analysis
 - (Q)SAR models
 - Standardized workflow
 - Automated workflow
- Depending on the situation, the most relevant data gap mechanism should be chosen, taking into account the following considerations:
 - Read-across is the appropriate data-gap filling method for “qualitative” endpoints like skin sensitisation or mutagenicity for which a limited number of results are possible (e.g. positive, negative, equivocal). Furthermore read-across is recommended for “quantitative endpoints” (e.g., 96h-LC50 for fish) if only a low number of analogues with experimental results are identified.
 - Trend analysis is the appropriate data-gap filling method for “quantitative endpoints” (e.g., 96h-LC50 for fish) if a high number of analogues with experimental results are identified.
 - “(Q)SAR models” can be used to fill a data gap if no adequate analogues are found for a target chemical.

In this example we will use the read-across approach.

Data Gap Filling Apply Read-across

The screenshot shows the QSAR Toolbox interface during a 'Data Gap Filling' operation. The 'Data Gap Filling' button in the top toolbar is highlighted with a red box and labeled '2'. A dialog box titled 'Possible data inconsistency' is open, showing 'Native scale/unit' options with 'Skin sensitisation II (ECETOC)' selected, and 'Gap filling scale/unit' options with 'Skin sensitisation II (ECETOC)' selected. The 'OK' button in the dialog is labeled '4'. In the 'Human Health Hazards' tree, 'Skin sensitisation II (ECETOC)' is selected, labeled '3'. In the table below, a row is highlighted in yellow, labeled '1'. The table shows data for various chemicals, including 'EC3' and 'Miscellaneous'.

Endpoint	Chemical	Data	Category
Skin sensitisation II (ECETOC)	EC3	17/44	M: 0.882 %
	Miscellaneous	37	M: Category C
Skin sensitization EC3(ratio)			M: 1.68 %
			M: Positive
Skin sensitization GHS (ordinal)			M: Negative
			M: Category 1A

1. Click on the row with the target endpoint and the cell corresponding to the target chemical; 2. Click **Read-across** button; 3. Select *Skin sensitisation II (ECETOC)*; 4. Click **OK**

Data Gap Filling Apply Read-across

The screenshot displays the QSAR Toolbox interface during a subcategorization process. The main window shows a list of chemical descriptors under 'Options', categorized into 'Empiric', 'Documented', and 'Simulated'. A 'Subcategorization' dialog box is open, showing 'Adjust options' for 'Target' and 'Analogues'. The 'Analogues' list shows selected items (3) [0%,10%], (2) [20%,30%], (1) [30%,40%], (1) [60%,70%], and (1) [80%,90%]. A 'Report' window shows a grid of chemical structures and their predicted categories. A 'log Kw' plot is visible at the bottom, showing the distribution of chemicals on a log scale from -10 to 15. A 'Select / filter data' and 'Subcategorize' button is highlighted in the bottom right corner.

Open **Select/filter data** and **Subcategorize** by: 1) *Protein binding alerts for skin sensitization by OASIS profiler* in combination with *Autoxidation simulator*, 2) Remove the different analogues; 3) *Structural similarity* 4) *Select* all analogues (3) similar less than 30% to the target chemical, by hold Ctrl button; 5) Click *Remove*

Data Gap Filling

Apply Category consistency elements

The screenshot displays the QSAR Toolbox interface. The top toolbar includes buttons for 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. The 'Category consistency' button is highlighted with a red box and callout '1'. Below it, the 'Category consistency wizard' is open, showing 'Wizard pages' on the left and configuration options for '2D/3D parameters' and 'Physico-chemical data'. The 'OK' button is highlighted with callout '2'. In the background, a data table shows chemical structures and their predicted values for various parameters. A 'Read-across prediction for EC3' plot is also visible. On the right, a 'Select / filter data' panel contains several buttons, with 'Accept prediction' highlighted by a green checkmark and callout '3'.

1 [target]	12	22	23
<chem>CCCCN</chem>	<chem>CCCCN</chem>	<chem>CCCCN</chem>	<chem>CCCCN</chem>
M: 0.882 %	M: 2.2 %	M: 2.2 %	M: 1.85 %
M: Category C	M: sensitising	M: Ambiguous	M: Category A
M: sensitising	M: sensitising	M: Positive	
No alert found	No alert found	No alert found	No alert found
No alert found	No alert found	No alert found	No alert found
No alert found	No alert found	No alert found	No alert found

After subcategorization process go back go the **Category definition** module and apply category elements* (1). No different selection than the default is needed – click **OK** (2). Once the category elements are applied **accept the prediction** (3).

*For more information on category elements see *Tutorial_1_TB 4.2. Category consistency*

Recap

- In the *Category definition* module you found analogues based on the alert with the best performance accounting for skin metabolism.
- In *Data gap filling* module you applied a read-across approach. Read-across is the appropriate data-gap filling method for “qualitative” endpoints like skin sensitisation. Since the most of the analogues and all five neighbouring tested chemicals in the category were positive, it was easy to accepting the prediction of positive for the target chemical.
- Category consistency was checked by applying the category elements.
- You are now ready to complete the final module and to create the report.
- Click “Report” to proceed to the last module.

Report Overview

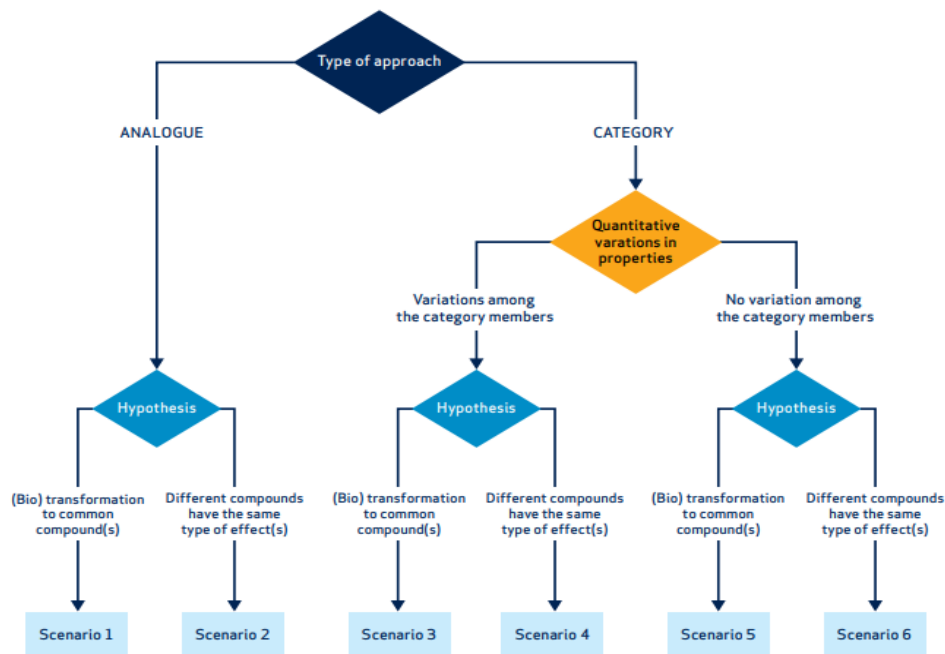
- Report module allows generating a report for any of the predictions performed within the Toolbox.
- The report module contains predefined report template which users can customize.
- Additionally specific RAAF scenario could be chosen. Selection of one of the scenarios will append automatically the related assessment elements related to the corresponding report sections.

Report

Selection of RAAF scenario

To select the applicable RAAF scenario for assessment, the following aspect should be identified*:

- the type of approach applied - analogue approach or category approach;
- the read-across hypothesis;
- For category approach - whether quantitative variations in the properties are observed among the category members must be considered.



*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf_en.pdf
 The OECD QSAR Toolbox for Grouping Chemicals into Categories

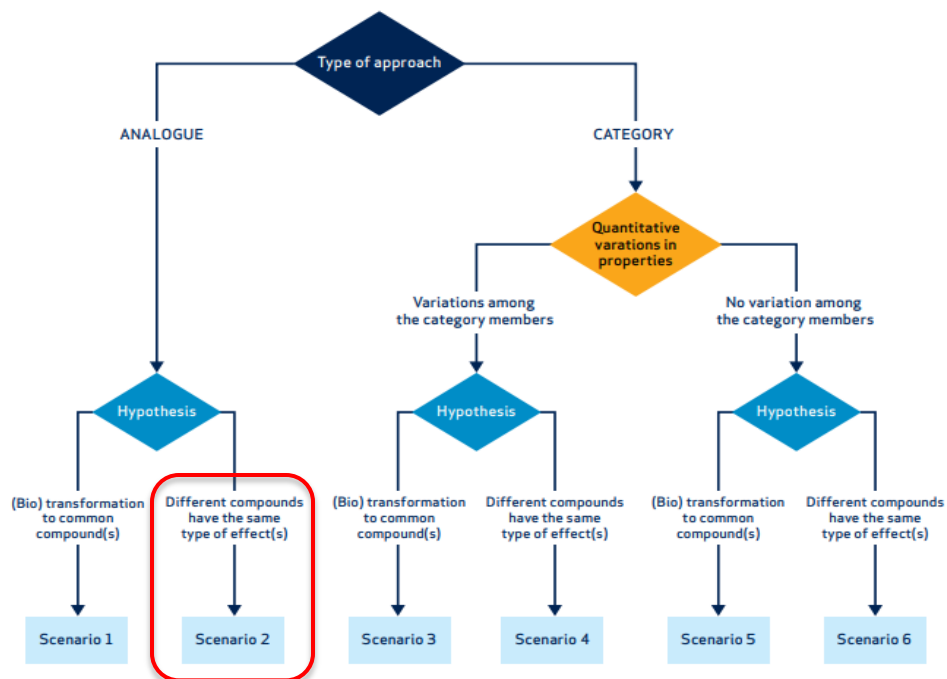
Report

Selection of RAAF scenario

For the current example:

- the type of approach applied - **analogue approach is used** (threshold of ≤ 3 analogues is proposed by LMC for the analogue approach) ;
- the read-across hypothesis – **different compounds with common underlying mechanism for metabolites of source and target substances** ;

Based on that Scenario II was identified as appropriated for the current example.



Read-Across Assessment Framework (RAAF) Scenario 2

- Scenario 2 covers the analogue approach for which the read-across hypothesis is based on different compounds with qualitatively similar properties.
- For the REACH information requirement under consideration, the property investigated in a study conducted with one source substance is used to predict properties that would be observed in a study with the target substance if it were to be conducted.
- The current case corresponds to Example 2 for Scenario 2 of the RAAF*. The target (B) and the source chemicals (A) are biotransformed to substances causing the same type of effects through a common mechanism (A1 and B1). The rest of the obtained compounds, non-common for the target and the source substance does not influence the prediction of the property under the consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A → A1 + A2	A1	A2
TARGET	B	B → B1	B1	-

*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

Report

Generation report according to RAAF-Scenario 2

The screenshot displays the QSAR Toolbox software interface. The top navigation bar shows the 'Report' module selected. The left sidebar has the 'Prediction' button highlighted with a red box and a callout '2'. The central area shows the 'Filter endpoint tree...' window with a tree structure of endpoints. A callout '1' points to the 'EC3' endpoint. The right side shows the 'Customize report content and appearance' dialog box. A callout '3' points to the 'Prediction' section, and a callout '4' points to the 'Add RAAF scenario' checkbox and the 'Scenario 2' dropdown menu. At the bottom, a blue box contains the following instructions:

1. Go to the **Report** module and click on the cell with the prediction;
2. Click the **Prediction** button;
3. Check the box at the top to add RAAF scenario;
4. Select **Scenario 2** from the drop-down menu.

Report

Generation report according to RAAF-Scenario 2

1

2

3

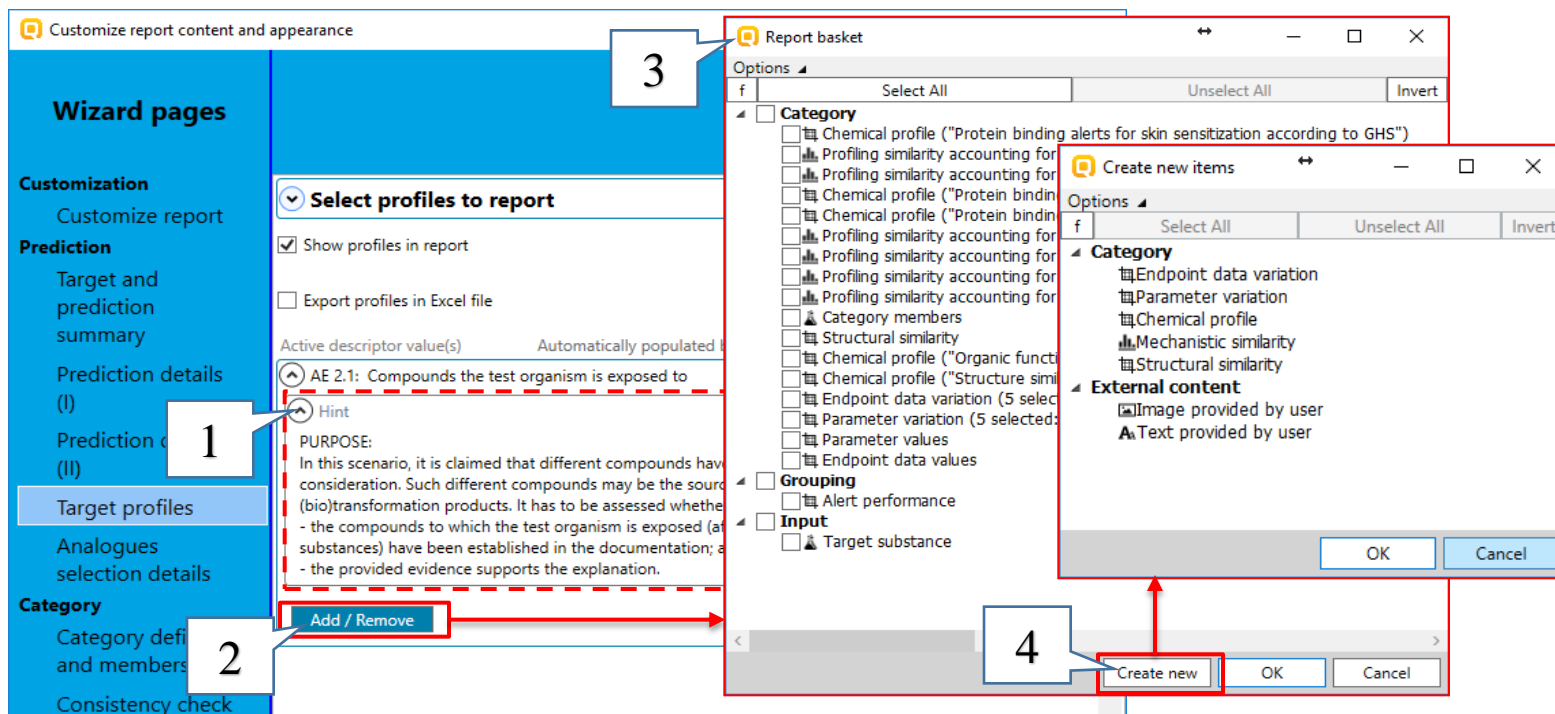
4

Once the RAAF scenario is selected (1) the assessment elements (AEs) related to it will be appended to the corresponding sections of the report automatically. AEs appear in the following report sections: **Target profiles** (2), **Category definition and members** (3) and **Consistency check** (4).

Each of the AEs will be considered in the next slides.

Report

Assessment elements of Scenario 2

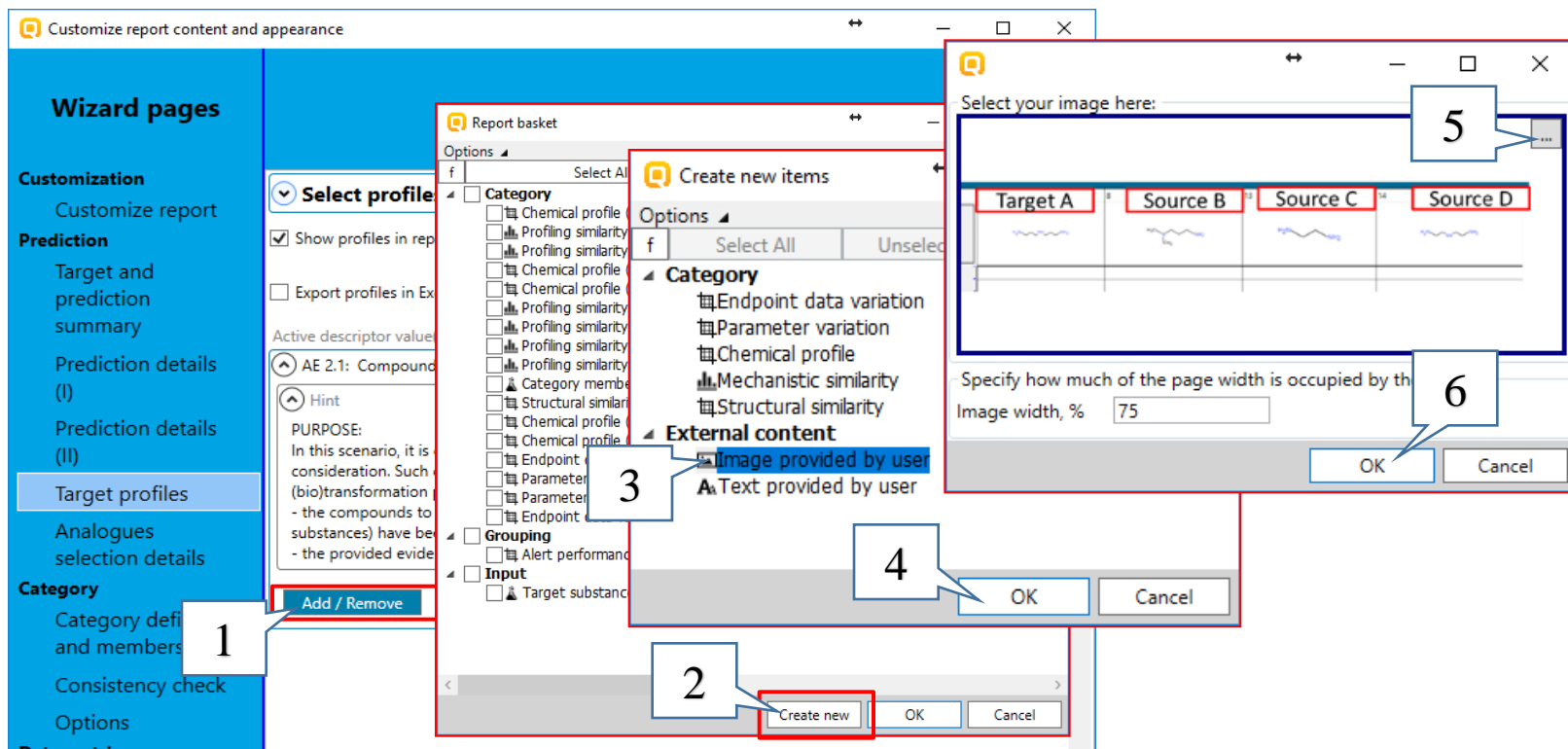


Hint for each of the assessment elements is available (1). Information can be included by clicking the **Add/Remove** button (2) located below the corresponding AE. The *Add/Remove* button invokes the so-called "**Report basket**" (3). The latter contain different items triggered by the actions of the user during the workflow (e.g. Alert performance calculation, applying of category elements, etc.). Additionally, new items (including items with external content) can be created (4).

Items with external content (picture and text) will be added for **AE 2.1. Compounds the test organism is exposed to**

Report

Assessment elements of Scenario 2

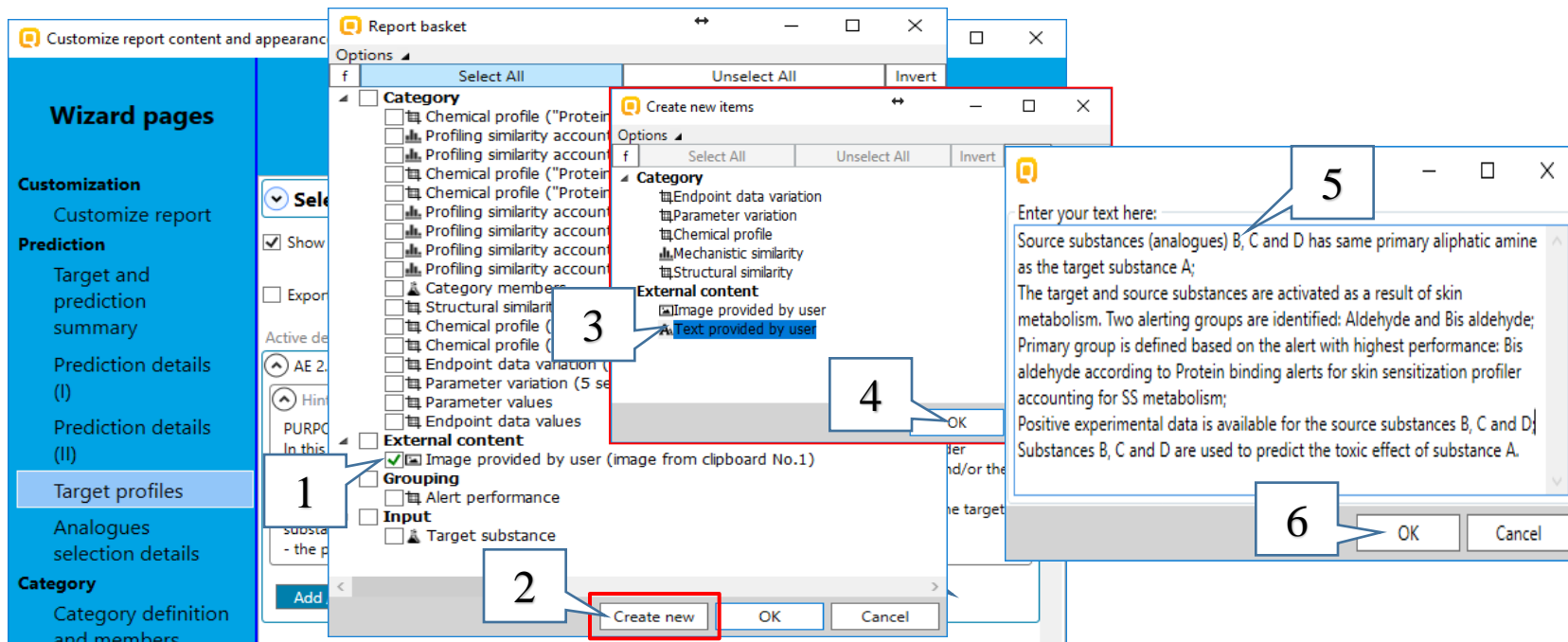


Click the **Add/Remove** button (1) and then **Create new** (2). Select to create an item with external content – **Image provided by user** (3) and click **OK** (4). New window appears where you can add your custom picture by Copy/Paste or browsing (5) to the directory in your PC where the desired picture is saved*. Finally confirm by **OK** (6).

*In the current example a picture illustrating the target chemical marked as **Target A** and source chemicals marked as **Source A, B** and **C** was prepared in advance.

Report

Assessment elements of Scenario 2



The newly created item appears in the *Report basket* (1). Now text will be also included. Click **Create new** (2), select **Text provided by user** (3) and click **OK** (4). Copy the following example text:

- *Source substances (analogues) B, C and D has same primary aliphatic amine as the target substance A;*
- *The target and source substances are activated as a result of skin metabolism. Two alerting groups are identified: Aldehyde and Bis aldehyde;*
- *Primary group is defined based on the alert with highest performance: Bis aldehyde according to Protein binding alerts for skin sensitization profiler accounting for SS metabolism;*
- *Positive experimental data is available for the source substances B, C and D (references for the data could be also included)*
- *Substances B, C and D are used to predict the toxic effect of substance A.*

and paste it in the new window (5). Finally confirm by **OK** (6).

Report Assessment elements of Scenario 2

Customize report content and appearance

Wizard pages

- Customization
 - Customize report
- Prediction
 - Target and prediction summary
 - Prediction details (I)
 - Prediction details (II)
 - Target profiles
 - Analogue selection
- Category
 - Category definition and members
 - Consistency check
 - Options
- Data matrix
 - Options

Select profiles to report

Show profiles in report

Export profiles in Excel file

Active descriptor value(s) Automatically populated by the system

AE 2.1: Compounds the test organism is exposed to

Hint

Add / Remove

1 Image provided by user (image from clipboard No.1) Edit Preview

2 Text provided by user (Target substance A and three source substances B, C and D) Edit Preview

3

Prediction of EC3 for Iminobis-3-propylamine 4 / 6

Target profiles
(OECD principle 5 - Chemical and biological mechanisms)

Profiles used for grouping/subcategorization

Using of "Skin metabolism simulator" Combined parent and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes (Protein binding alerts for skin sensitization by OASIS) (primary grouping)	Parent and 5 metabolites; Has all of the required categories: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis aldehydes; Has the following additional categories: No alert found, Schiff base formation, Schiff base formation >> Schiff base formation with carbonyl compounds, Schiff base formation >> Schiff base formation with carbonyl compounds >> Aldehydes
Protein binding alerts for skin sensitization by OASIS with Autoxidation simulator (subcategorization)	No alert found
Structure similarity (subcategorization)	[90%,100%]
log Kow (calculated): -1.15	

AE 2.1: Compounds the test organism is exposed to

1. Image provided by user (Image from clipboard No.1)

Target A	Source B	Source C	Source D
<chem>CCN</chem>	<chem>CCN</chem>	<chem>CCN</chem>	<chem>CCN</chem>

Target substance A and three source substances (B, C and D); Source substances (analogues) B, C and D has same primary aliphatic amine as the target substance A; The target and source substances are activated as a result of skin metabolism. Two positive alerting groups are obtained: Aldehyde and Bis aldehyde; Primary group is defined based on the alert with highest performance: Bis aldehyde according to Protein binding alerts for skin sensitization profiler accounting for SS metabolism; Substances B, C and D are used to predict the toxic effect of substance A.

4

QSAR Toolbox 4.2 Database version: 4.2 QSAR TOOLBOX TPRF v4.2

Both newly created items appear under the **AE 2.1**. (1). Each of the items can be edited (2) or just previewed (3) in a .pdf format. Example of how the AE 2.1. and related description will look in the generated report is shown on the right (4).

Report Assessment elements of Scenario 2

Customize report content and appearance

Wizard pages

Customization

Customize report

Prediction

Target and prediction summary

Prediction details (I)

Prediction details (II)

Target profile

Analogues selection

Category

Category definition and members

Consistency check

Options

Data matrix

Options

Profiles/Metabolisms

Category members

AE A.1: Characterisation of source substance

Hint

PURPOSE:
The substance which is used as the source substance needs to have a clear substance characterization. It has to be assessed whether:
- the chemical identity of the analogue is sufficiently clear for a meaningful assessment of the proposed read-across; and
- the impurity profile is clear.

Name, CAS and/or EC number, chemical structure should be provided.

Add / Remove

Category members

Preview

Purity / Impurity

AE A.1: Characterisation of source substance

Hint

PURPOSE:
Impurity profiles for the source substance should be provided (with identifiers as defined above).

Add / Remove

AE A.3: Reliability and adequacy of the source study

Hint

Add / Remove

Back Next Cancel Create report

1.5. Category members

AE A.1: Characterisation of source substance

3

Category members				
#	CAS	Name	SMILES	Structure
1	56-18-8	Iminobis-3-propylamine	NCCCNCCCN	<chem>NCCCNCCCN</chem>
2	109-55-7	3-aminopropyl dimethylamine	CN(C)CCCN	<chem>CN(C)CCCN</chem>
3	107-15-3	Ethylenediamine	NCCN	<chem>NCCN</chem>

QSAR Toolbox 4.2 Database version: 4.2

QSAR TOOLBOX TPRF v4.2

Chemicals category 3 / 30

4	111-40-0	Diethylenetriamine	NCCNCCN	<chem>NCCNCCN</chem>
---	----------	--------------------	---------	----------------------

Purity / Impurity manually editable field

Not provided by the user

AE A.1: Characterisation of source substance

Not provided by user

Two AE (AE A.1 and A.3) related to Scenario 2 are included in the *Category definition and members* section.

- **AE A.1 Characterization of source substance** is automatically filled by the system using the available items in the *Report basket*. In this example *Category members* item (1) is appended, only. If impurities/additives of the used analogues are available, they will appear under the **AE A.1** in *Purity / Impurity* (2). The current analogues have no additives/impurities. Example of how the AE A.1. will look in the generated report is shown on the right(3).
- **AE A.3 Reliability and adequacy of the source study** should be filled in manually (4) (see on the next slide)

Report Assessment elements of Scenario 2

AE A.3: Click the **Add/Remove** button (1) and create new item with textual content (2) (see slide 52).

In the text field paste the following example text:

*"The all three source substance are tested according to the Local lymph node assay (LLNA)
The study is used to predict the skin sensitization effect concerning LLNA study for the target substance"*

Additionally a snapshot of the filter by test conditions window (2) could be added to confirm the consistency regarding the assay.

Report Assessment elements of Scenario 2

Customize report content and appearance

Wizard pages

Customization
 Customize report

Prediction
 Target and prediction summary
 Prediction details (I)
 Prediction details (II)
 Target profiles
 Analogues selection details

Category
 Category definition and members
 Consistency check
 Options

Data matrix
 Options

Profiles/Metabolisms

Category members

AE A.1: Characterisation of source substance

Purity / Impurity

AE A.1: Characterisation of source substance

AE A.3: Reliability and adequacy of the source study

Hint

PURPOSE:
 The source study needs to match the default REACH requirements in terms of reliability and adequacy as requested for any other key study. It has to be assessed whether:

- the study design reported for the source study is adequate and reliable for the purpose of the prediction based on read-across;
- the study design should cover the key parameters in the corresponding test method referred to in Article 13(3);
- the study design should cover an exposure duration comparable to or longer than the corresponding method referred to in Article 13(3); and
- there is adequate and reliable documentation of the applied test method, i.e. a robust study summary should be provided. The test material used represents the source substance as described in the hypothesis in terms of purity and impurities.

Add / Remove

Text provided by user (• The all three source substance are Edit Preview)

Image provided by user (image from clipboard No.1) Edit Preview

Back Next Cancel Create report

AE A.3: Reliability and adequacy of the source study

- The all three source substance are tested in a local lymph node assay (LLNA)
- The study is used to predict the skins sensitization effect concerning LLNA study for the target substance

Image provided by user (image from clipboard No.1)

QSAR Toolbox 4.2 Database version: 4.2 **QSAR TOOLBOX** TPRF v4.2

Chemicals category 3 / 12

The screenshot shows the QSAR Toolbox interface with a data matrix table and a graph. The data matrix table has columns for 'Chemical', 'Category', 'Purity', 'Impurity', and 'Score'. The graph plots 'Score' on the y-axis (ranging from 0.00 to 1.00) against 'LogP' on the x-axis (ranging from 0.00 to 1.00). A legend indicates 'Best and worst predicted QP's based on QP's from the QSAR Toolbox v4.2.0 (TPRF v4.2.0)'. A 'Check this data' button is visible in the bottom right corner.

Example of how the **AE A.3.** will look in the generated report is shown on the right.

Report Assessment elements of Scenario 2

The screenshot shows a window titled "Customize report content and appearance" with a sidebar on the left containing "Wizard pages" such as "Customization", "Prediction", "Category", and "Data matrix". The main area displays three assessment elements (AEs) with their purposes and hints. Red arrows point from the text boxes on the right to the corresponding AE sections in the screenshot.

- AE 2.4: Exposure to other compounds than to those linked to the prediction**
 Hint: Other compounds than those linked in the hypothesis to the prediction may be formed via other (bio)transformation pathways or may be intermediates/metabolites of the identified pathway. In addition, the impurity profiles associated with the source and target substances may have an impact on the prediction. The other compounds may have been identified by the hypothesis, but not linked to the prediction. Another possibility is that the occurrence of such compounds has been identified by the assessing expert. It has to be assessed whether:
 - other compounds that those linked to the prediction may be formed (e.g. via another (bio)transformation pathway or as intermediates) or are present as impurities (see AE A.1); and
 - indications are available that such compounds could influence the prediction of the property under consideration.
- AE 2.5: Occurrence of other effects than covered by the hypothesis and justification**
 Hint: It has to be assessed whether:
 - additional mechanisms than those identified in the hypothesis may be acting on the basis of mechanistic insights or derived from information in the data matrix; and
 - these additional mechanisms affect the prediction for the property under consideration.
- AE A.4: Bias that influences the prediction**
 Hint: It has to be assessed whether:
 - it is clear from the documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded;
 - there are additional, structurally-similar substances which are currently not used in the analogue approach and which arguably could be used;
 - there is readily-available information from these additional substances;
 - this information is biologically significantly different for relevant properties in comparison with the existing analogue(s); and
 - these differences decrease the confidence in the prediction (possibility of underestimation of hazard).

Example text for **AE 2.4. Exposure to other compounds than to those linked to the prediction:**

- Target substance A and source substances B,C and D are all metabolized to aldehydes and bis aldehydes;
- Bis aldehydes functionality is responsible for the toxic effect;
- Aldehydes are not expected to cause skin sensitization effect by the expert knowledge;
- The latter is confirmed with the smaller value of alert performance of the group

Example text for **AE 2.5. Occurrence of other effects than covered by the hypothesis and justification:**

- Target substance A and source substances B,C and D are metabolized by skin metabolism simulator;
- Protein binding alerts (PBA) for skin sensitization are identified in the metabolites of the target and source substances;
- No PBA for chromosomal aberration are identified in the target and source substances, nor in the structures of their metabolites.

Example text for **AE A.4. Bias that influences the prediction:**

- Alert performance is used to define the alert with the best prediction purposes with respect to the target endpoint. Bis aldehyde functionality is selected for searching for analogues.
- All identified analogues that have PBA as a result of Autoxidation simulator are removed. The most dissimilar chemicals (with similarity below 30%) are also removed. Expert can provide additional literature search of similar analogues with similar effects.

Six AEs are included to the *Consistency check* section. Example content for the first three AEs is given.

Report

Assessment elements of Scenario 2

Customize report content and appearance

Wizard pages

- Customization
- Prediction
 - Target prediction summary **1**
 - Prediction details (I)
 - Prediction details (II)
 - Target profiles
 - Analogue selection details
- Category
 - Category definition and members
 - Consistency check
 - Options
 - Data matrix
 - Options **2**

Structural similarity

Justification for selected structure similarity profilers

Add / Remove

- Structural similarity Edit Preview
- Chemical profile ("Organic functional groups, Norbert Haider (checkmc Edit Preview
- Chemical profile ("Organic functional groups") Edit Preview
- Chemical profile ("Structure similarity") Edit Preview

Comments on structural similarity

AE A.2: Link of structural similarity and differences with the proposed prediction

Hint

PURPOSE:
The aim of this AE is to verify that the source and target substances are covered by the read-across hypothesis. It has to be assessed whether:

- the scientific hypothesis establishes the structural similarities and differences of source and target;
- structural similarities and differences are linked with the possibility to predict similar properties; and
- the provided evidence supports the proposed link between structural similarities and the possibility to predict.

Add / Remove

Calculated structure similarity

	Chemical 1	Chemical 2	Chemical 3	Chemical 4
Chemical 1	100%	37.5 %	61.5 %	87.5 %
Chemical 2	37.5 %	100%	36.4 %	28.6 %
Chemical 3	61.5 %	36.4 %	100%	72.7 %
Chemical 4	87.5 %	28.6 %	72.7 %	100%

Chemical profile ("Organic functional groups")

1	2	3
<chem>NCCNCCN</chem>	<chem>CCN(C)CCN</chem>	<chem>NCCN</chem>
Amine, primary Amine, secondary Aliphatic amine, primary Aliphatic amine, secondary	Amine, primary Amine, tertiary Aliphatic amine, primary Aliphatic amine, tertiary	Amine, primary Aliphatic amine, primary
<chem>NCCNCCN</chem>		
Amine, primary Amine, secondary Aliphatic amine, primary Aliphatic amine, secondary		

AE A.2. Link of structural similarity and differences with the proposed prediction is related to the structural similarity of the final category.

All items in the report basket related to the structural consistency of the category (1) are added automatically.

The following example text can be added for AE A.2. (2) by analyzing the structural similarity items:

- *Structural similarity between Target substance A and 3 source substances B, C and D according to Str.similarity profiler is in the range of [29-88%]*
- *They all have primary aliphatic amine based on the OFG profiler, while the target substance A and source substance D have additional secondary aliphatic amine and the source substance B has additional tertiary amine functional group.*

Report Assessment elements of Scenario 2

Alert performance
Scale=Skin sensitisation II (ECETOC); Endpoint=EC3; Metabolism=Skin metabolism simulator

#	Alert name	Alert performance, %		Number of chemicals	
		Positive	Negative	Positive	Negative
1	Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found<AND>Aldehydes<AND>Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	78.57	21.43	11	3
2	Using of "Skin metabolism simulator" Combined parent and products requirements: No alert found (Protein binding alerts for skin sensitization by OASIS)	45.35	54.65	575	693
3	Using of "Skin metabolism simulator" Combined parent and products requirements: Aldehydes (Protein binding alerts for skin sensitization by OASIS)	48.99	51.01	169	176
4	Using of "Skin metabolism simulator" Combined parent and products requirements: Bis aldehydes (Protein binding alerts for skin sensitization by OASIS)	82.35	17.65	14	3

AE A.2.2. Common underlying mechanism, qualitative aspects is related to the mechanistic similarity of the final category.

All items in the report basket related to the mechanistic consistency of the category (1) are added automatically. Only the Alert performance item have to be included here manually (2). Right-click on Alert performance in order to preview it.

The following example text summarizing the results of the provided mechanistic similarity items can be added:

- *Target substance A and source substances B, C and D are all metabolized to Bis aldehydes*
- *Bis aldehydes is taken as alerting groups responsible for the toxic effect based on the expert knowledge*
- *Bis aldehydes are taken as alerting group supported by the higher alert performance (82 %) as compared with aldehyde group (47%)*

Additionally, metabolic maps (for each of the analogues), produced by external software or found in the literature, could be included to AE in order to support the mechanistic similarity of the category.

Report Assessment elements of Scenario 2

Customize report content and appearance

Wizard pages

- Customization
 - Customize report
- Prediction
 - Target and prediction summary
 - Prediction details (I)
 - Prediction details (II)
 - Target profiles
 - Analogues selection details
- Category
 - Category definition and members
 - Consistency check
- Data matrix
 - Options

AE 2.2: Common underlying mechanism, qualitative aspects

Hint

Add / Remove

Alert performance Preview

Additional endpoints

Tree position:
Human Health Hazards#Sensitisation

Data filters:

Category values for selected additional endpoints

Comments on additional endpoints

Additional comments

AE 2.3: Common underlying mechanism, quantitative aspects

Hint

PURPOSE:
Under this scenario, there should be no biologically significant quantitative differences for the same type of effects caused by the underlying mechanism or the differences should be used in a conservative prediction (i.e. effects for the target substance are not likely to be under-predicted, worst case approach). It has to be assessed whether:

- the documentation has provided an explanation why a common underlying mechanism leads to the same quantitative outcome (for source and target) with regard to the prediction of the property under consideration; and
- the provided evidence supports the explanation.

Add / Remove

Back Next Cancel Create re

AE A.2.3. Common underlying mechanism, quantitative aspects

is also related to the mechanistic similarity of the final category. The following information could be included here:

- 1) textual or illustrated explanation why the common underlying mechanism leads to the same quantitative outcome (for source and target) with regard to the prediction of the property under consideration; and

Example text:

- Target substance A is metabolized to Aldehydes and Bis aldehydes
- It is expected that Bis-aldehydes as the alert with higher alert performance is could be responsible for the toxic effect
- Source substances B, C and D are metabolized to aldehydes and bis-aldehydes, too
- The available experimental EC3 values for the source substances corresponds to a positive effect.
- Similar toxic effects observed in sources substances supports the prediction for the target
- Toxic effects of all source substances and target are supported by the identified additional SS data

2) evidences supporting the explanation.

Include all available SS EC3 data for the target chemical and the source substances in all Toolbox database. See how to do this on the next two slides.

Report Assessment elements of Scenario 2

Click **Add/Remove** button (1) and **create new** item (2). Select **Endpoint data variation** (3) and confirm by **OK** (4). A new window with the endpoint tree organization appears. Select **EC3** and click **OK** (5). This new item will provide information not only for the used, but for all available EC3 data for the chemicals of the category.

Report

Assessment elements of Scenario 2

AE 2.3: Common underlying mechanism, quantitative aspects

Endpoint data variation (1 selected: Human Health Hazards#Sensitisation#[s]Endpoint:EC3#[s]Assay:LLNA#[s]Type of method:in Vivo#[s]Organ:Skin)
Human Health Hazards data variation

Position	Variation	unit (family)
Sensitisation#Skin#in Vivo#LLNA#EC3	0.882 ÷ 5.8	%(Skin sensitization EC3(ratio))

Target substance A is metabolized to Aldehydes and Bis aldehydes
 It is expected that Bis-aldehydes as the alert with higher alert performance is could be responsible for the toxic effect
 Source substances B, C and D are metabolized to aldehydes and bis-aldehydes, too
 Similar toxic effects observed in sources substances supports the prediction for the target
 Toxic effects of all source substances and target are supported by the identified additional SS data

After creating of the new item, it appears below the AE 2.3, along with the created text item (1). Example on how the **AE 2.3**, will look in the generated report is shown in right (2).

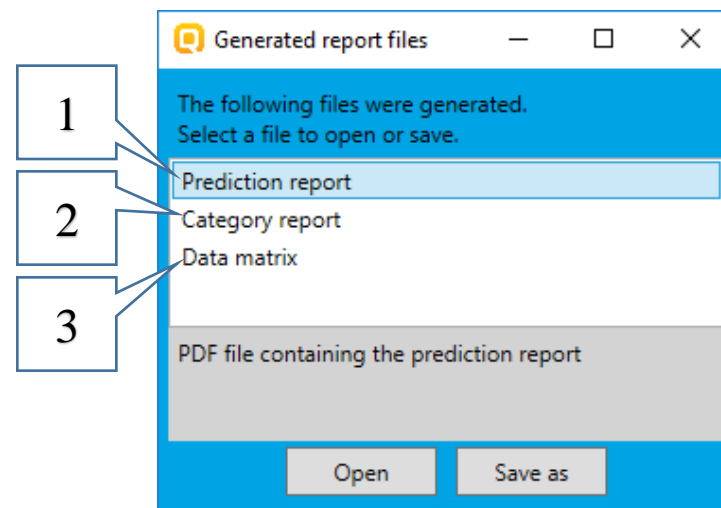
Report Generation

After clicking *Create report* button, *Generated report files* window appears. It contains three type of files:

- 1) Prediction report** - a PDF file containing the prediction information related to the target.
- 2) Category report** - a PDF file containing information for the consistency of the final category (target plus used analogues)
- 3) Data matrix** - a MS Excel file containing chemicals used for prediction along with their data for selected parameters, profiles and endpoint tree positions.

RAAF AEs are included in the first two files.

All generated files should be provided when submit a prediction.



Report Generated report files

Prediction of EC3 for Iminobis-3-propylamine 1 / 6

Prediction report

QSAR Toolbox prediction for single chemical

(In accordance with RAAF scenario 2)

Date: 20 Mar 2018
Author(s):
Contact details:

Target information		
Structural Information	Numerical Identifiers	Chemical names
SMILES: NCCCNC	CAS#: 56-18-8 Other: EC Number:3774080	1,3-Propanediamine, N-(3-aminopropyl)- 1,3-Propanediamine, N1-(3-aminopropyl)- 1,3-propanediamine, n-(3-aminopropyl)-
Structure <chem>NCCNC</chem>		

Prediction summary

Predicted endpoint: EC3; No effect specified; No species specified; No duration specified; No guideline specified

Resulted value: 2.32 (from -1.15 to 6.61)

Chemicals category 1 / 31

Category report

QSAR Toolbox report for category

(In accordance with RAAF scenario 2)

1. Category definition

1.1. Category definition manually editable field
Not provided by the user

Ranges for selected physicochemical properties and calculated parameters

Parameter variation (5 selected: Boiling point; log Kow; Molecular Weight; Vapor Pressure (Antoine method); Water Solubility)
2D parameters data variation

Parameter name	Variation	unit (family)
Boiling point	103 ÷ 228	°C
log Kow	-2.13 ÷ -0.45	<no units>
Molecular Weight	60.1 ÷ 131	Da
Vapor Pressure (Antoine method)	0.0913 ÷ 19	mm Hg
	1E+06	mg/L

Data matrix report

	Target chemical	Neighbour #1	Neighbour #2	Neighbour #3
Substance identity				
Structure	<chem>NCCNC</chem>	<chem>NCCCNC</chem>	<chem>NCCNC</chem>	<chem>NCCNC</chem>
CAS number	56-18-8	109-55-7	107-15-3	111-40-0
Chemical name	iminobis-3-propylamine	3-aminopropylidimethylamine	Ethylendiamine	Diethylenetriamine
Other identifier				
SMILES	NCCCNC	CNCCCNC	NCCNC	NCCCNC
Parameters	unit			
Vapor Pressure (Antoine method)	mm Hg	9.41	19	0.274
log Kow	-1.15	-0.45	-1.62	-2.13
Molecular Weight	Da	102	60.1	103
Boiling point	°C	228	134	189
Water solubility	mg/L	1E+06	1E+06	1E+06
Profiles				
Profiles used for grouping/subcategorization				
Using of "skin metabolism simulator" Combined	Parent and 5 metabolites;	Parent and 12 metabolites;	Parent and 5 metabolites;	Parent and 5 metabolites;
Protein binding alerts for skin sensitization by structure similarity (subcategorization)	No alert found [90%,100%]	No alert found [30%,40%]	No alert found [60%,70%]	No alert found [80%,90%]
Endpoint Specific				
Protein binding alerts for skin sensitization by structure similarity (subcategorization)	No alert found	No alert found	No alert found	No alert found
Protein binding alerts for skin sensitization by structure similarity (subcategorization)	No alert found	No alert found	No alert found	No alert found
Protein binding alerts for skin sensitization by structure similarity (subcategorization)	No alert found	No alert found	No alert found	No alert found
Empiric				
Organic functional groups	Amine, primary; Amine, secondary	Amine, primary; Amine, tertiary	Amine, primary; Aliphatic amine, primary	Amine, primary; Amine, secondary
Measured and predicted data				
Data used for prediction				
environment	endpoint	value	unit	species, duration, test type, type of method, assay, strain, test
		value	unit	species, duration, test type, type of method, assay, strain, test
		value	unit	species, duration, test type, type of method, assay, strain, test
		value	unit	species, duration, test type, type of method, assay, strain, test
Sensitisation	EC3	2.32	%	in Vivo mouse
Sensitisation	EC3	2.2	%	in Vivo mouse

variation (4 selected: Physical Chemical Properties#Boiling point; Physical Chemical Properties#Vapor pressure; Physical Chemical Properties#Water solubility; Physical Chemical Properties#Octanol/Water Partition Coefficient:#N-Octanol/Water)

Physical Properties data variation

in	Variation	unit (family)
	117 ÷ 207	°C(Temperature)
	NOT_SPECIFIED	HT Version 20120101 phrasegroup_C47
	0.0126 ÷ 99.8	bar(Pressure)
	5.9 ÷ 1.25E+03	Pa(Pressure)
	0.232 ÷ 12	mm Hg(Pressure)
	1E+06	mg/L(Mass concentration)
	1E+06	mg/L(Mass concentration)
N-	-4.96 ÷ -0.352	

get endpoint(s) manually editable field

QSAR TOOLBOX TPRF v4.2

Congratulation

- You have now been introduced to the RAAF scenario;
- You have now been introduced to the *Report basket*.
- You have now been introduced to the AEs related to Scenario 2.
- Note proficiency comes with practice.