

## OECD QSAR Toolbox v.4.2

An example illustrating RAAF Scenario 5 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 assessing of the outcome whether read across is scientifically acceptable or not
- 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;
- Relevancy of profiles and data availability;
- 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 5;
- To explain to the user how to search for analogues producing common metabolite;
- To introduce to the user the read across assessment elements (AE) and to provide examples with possible content of them;
- To introduce to the user the report basket;
- To provide 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 has been developed by ECHA as an 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).
- Total six scenarios are available: two for analogue approach and four for category approach

# Read Across Assessment Framework (RAAF)

## Criteria for the different RAAF scenarios

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](https://echa.europa.eu/documents/10162/13628/raaf_en.pdf)

# Read Across Assessment Framework (RAAF)

## Selection of RAAF scenario

1. Distinguish whether analogue or category approach is decided based on number (N) of analogues\*:
  - a) N of analogues  $\leq 3$  is Analogue approach (scenario 1-2)
  - b) N of analogues  $> 3$  is Category approach (scenario 3-6)
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 (scenario 3-6) there is a need to take further account whether or not quantitative variations in the properties are observed among the category members:
  - a) There is quantitative variation in the (eco) toxicity when it is more than 1 log units\*\* (scenario 3 and 4)
  - b) Quantitative variation is not expected in the (eco) toxicity when it is less or equal to 1 log unit (scenario 5-6)

\* The threshold for number of analogues which distinguishes analogue from category approach is proposed by LMC

\*\*The quantitative variation in the (eco)toxicity of 1 log unit is proposed by LMC due to empirically observations.

# 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](https://echa.europa.eu/documents/10162/13628/raaf_en.pdf)

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## The Exercise

- In this exercise we will predict *Repeated dose toxicity* of Eugenol [CAS# 97-53-0], which will be the “target” chemical;
- The target endpoint will be preliminary defined;
- The category will be defined based on analogues having common metabolite produced after *in vivo* Rat liver metabolism;
- A read-across approach will be used for the prediction. The prediction will be based on category approach relying on common metabolite generated for the 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.

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- The example
- **Workflow**

# 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 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

## Input target chemical by CAS#

The screenshot illustrates the steps to input a target chemical by its CAS number in the QSAR Toolbox. The interface shows the 'Input' menu option highlighted, and a search dialog box where the CAS number '97530' is entered. The search results table is as follows:

1	CAS	97-53-0
	SMILES	<chem>COc1cc(CC=C)ccc1O</chem>
	CS Relation	High
<input checked="" type="checkbox"/>	Substance	Mono constituent
	Composition	
	Name	[eugenol eugenol (4-allyl-2-...  phenol, 2-methoxy-4-(2-pr...  1-ALLYL-3-METHOXY-4-...

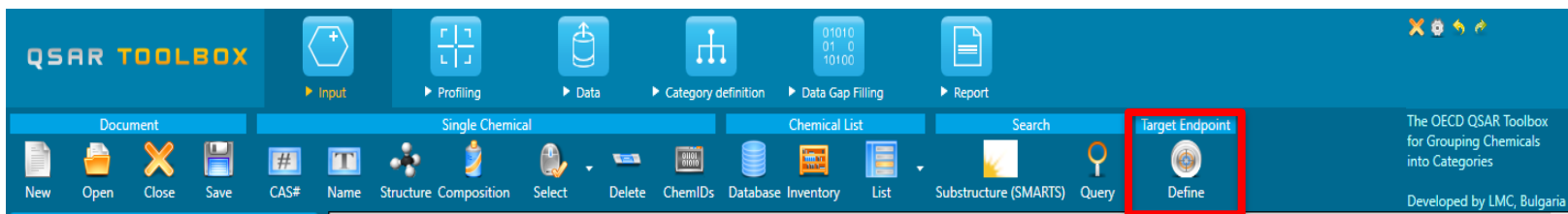
The chemical structure shown is 4-allyl-2-methoxyphenol (Eugenol), which consists of a benzene ring with a methoxy group (-OCH<sub>3</sub>) and a hydroxyl group (-OH) in the ortho position, and an allyl group (-CH<sub>2</sub>-CH=CH<sub>2</sub>) in the para position.

1. Click **CAS#**; 2. Enter the **CAS# 97-53-0** in the blank field; 3. Click **Search**; 4. When the structure with the requested CAS # appears, click **OK**.

# Input

## Define target endpoint

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



# Input

## Define target endpoint

The screenshot displays the QSAR Toolbox software interface. The top toolbar features a 'Target Endpoint' button (1) and a 'Define' button. Below the toolbar, the 'Documents' panel shows a document with CAS: 97530. Two 'Select endpoint' dialog boxes are overlaid. The first dialog (2) shows a tree view of endpoint categories, with 'Repeated Dose Toxicity' selected. The 'Next' button (3) is visible at the bottom. The second dialog (4) shows the configuration for 'Repeated Dose Toxicity'. The 'Test organisms (species)' dropdown (5) is set to 'Rat', and the 'Endpoint' dropdown (4) is set to 'NOAEL'. The 'Finish' button (6) is highlighted at the bottom right.

When click on **Define** (1) you should select the target endpoint. Select **Repeated Dose Toxicity** in the *Human health hazards level* (2) and click on **Next** (3). Select **NOAEL** endpoint (4) and **Rat** test organism (5) from the drop-down menus. 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 yellow highlighted.

The screenshot displays the QSAR Toolbox software interface. The top menu bar includes options like 'Document', 'Single Chemical', 'Chemical List', 'Search', and 'Target Endpoint'. The 'Target Endpoint' menu is active, showing a list of endpoints. The 'Repeated Dose Toxicity' endpoint is expanded, and the 'Rat' sub-endpoint is further expanded, with the 'NOEL' row highlighted in yellow. A red box highlights the 'Repeated Dose Toxicity - Rat - NOEL' endpoint. The chemical structure of the target compound is shown in the top right corner of the interface.

# Data Overview

- “Data” refers to the electronic process of retrieving the environmental fate, eco-toxicity 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 interface. The top toolbar has a 'Data' icon (1). Below it, the 'Data' module is active, showing a 'Gather' button (3). On the left, the 'Databases' list has 'ECHA CHEM' and 'Food TOX Hazard EFSA' highlighted in green (2). A 'Read data?' dialog box is open, showing a list of toxicity endpoints. The 'Repeated Dose Toxicity' checkbox is checked (4). The dialog also shows a chemical structure of a target molecule.

1. Go to **Data** module
2. Select both green highlighted databases – **ECHA CHEM** and **Food TOX Hazard EFSA**;
3. Click **Gather**.
4. Choose to collect repeated dose toxicity data, only

# 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 is performed only among the chemicals which are listed in the selected databases. In this example ECHA CHEM and *Food TOX Hazard EFSA* databases are selected.
- In this example, an insert window appears stating there are 23 experimental data points for the target chemical. Six data points (varying from 67 mg/kg bdwt/d to 1250 mg/kg bdwt/d) are available for the defined target endpoint. We will try to reproduce the worst case scenario (67 mg/kg bdwt/d).
- Go to the *Profiling* module to check for the reason of the possible effect (to check for an alert identified in the target chemical).



# Profiling Overview

- “Profiling” refers to the electronic process of retrieving relevant information for the target compound, other than its environmental fate, ecotoxicity and toxicity data, which are stored in the Toolbox databases.
- Available information includes probable mechanism(s) of action, as well as observed or simulated metabolites.
- Based on the “profilers’ relevancy” the most suitable ones are getting colour highlighted\*
- For the purpose of this example suitable profilers in combination with simulators are used (see next slide)

\*For more details regarding relevancy of profilers see ppt: *Example for predicting skin sensitization taking into account alert performance*

# Profiling

## Profiling the target chemical

The screenshot displays the QSAR Toolbox Profiling module. The top navigation bar includes buttons for 'Input', 'Profiling', 'Category definition', 'Data Gap Filling', and 'Report'. The 'Profiling' button is highlighted with a callout box labeled '1'. Below the navigation bar, the 'Documents' section contains 'Apply', 'View', 'New', and 'Delete' buttons. The 'Apply' button is highlighted with a callout box labeled '3'. The 'Profiling methods' section is expanded, showing a list of options. The 'Repeated dose (HESS)' option is checked, and the 'in vivo Rat metabolism simulator' option is also checked. The 'Metabolism/Transformations' section is also expanded, showing a list of options. The 'in vivo Rat metabolism simulator' option is checked. On the right side, the 'Filter endpoint tree...' window is open, showing a tree structure of endpoints. The 'NOAEL' endpoint is highlighted in yellow. The chemical structure of the target chemical is shown in the top right corner.

1. Go to the **Profiling** module;
2. Select *Repeated dose (HESS)* profiling scheme and *in vivo Rat metabolism simulator*;
3. Click on **Apply**

# Profiling

## Profiling results

The screenshot displays the QSAR Toolbox interface. The top navigation bar includes 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. The left sidebar shows 'Profiling methods' and 'Metabolism/Transformations' sections. The main window, 'Filter endpoint tree...', shows a tree structure of endpoints. The 'Structure' column shows a chemical structure of a target molecule. The 'Filter endpoint tree...' window is filtered to show '1 [target]'. The tree structure includes endpoints such as 'Neurotoxicity', 'Photoinduced toxicity', 'Repeated Dose Toxicity', 'Sensitisation', 'Toxicity to Reproduction', 'Toxicokinetics, Metabolism and Distributi...', 'Profile', 'Toxicological', 'Metabolism/Transformations', and 'in vivo Rat metabolism simulator'. The 'Repeated dose (HESS)' endpoint under 'Toxicological' is highlighted with a red box and callout 1. The 'in vivo Rat metabolism simulator' endpoint is highlighted with a red box and callout 2. The 'Repeated dose (HESS)' endpoint under 'Toxicological' is highlighted with a red box and callout 3.

- 1) No alerts are identified in the target structure as a parent;
- 2) 9 metabolites are generated as a result of *in vivo Rat metabolism simulator*;
- 3) Alerts for repeated dose toxicity are identified in four of the generated metabolites.

## Recap

- In module *Input*, 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 experimental data for the target available in the selected database.
- In the *Profiling* module, you profiled the target chemical with profiling scheme and metabolic simulator related to the selected target endpoint.
- Alerts for repeated dose toxicity were identified for some of the metabolites produced by simulating of metabolic activation.

# Handling of in vivo rat liver metabolism

The screenshot displays the QSAR Toolbox software interface. The top menu bar includes options like 'Input', 'Profiling', 'Data', 'Chemical List', 'Data Gap Filling', and 'Report'. Below this is a toolbar with icons for 'New', 'Open', 'Close', 'Save', 'CAS#', 'Name', 'Structure', 'Composition', 'Select', 'ChemIDs', 'Database Inventory', 'List', 'Substructure (SMARTS)', 'Query', and 'Define'. The main workspace is divided into several panes. On the left, a 'Documents' pane shows a tree view with 'Document 1' containing a chemical with CAS# 97530. A right-click context menu is open over this document, with 'Multiplication' selected, and its sub-menu 'Metabolism/Transformations' is also open. Within this sub-menu, the 'in vivo Rat metabolism simulator' option is highlighted with a red box. The central pane shows a 'Filter endpoint tree...' with a search filter '1 [target]'. The right pane displays the chemical structure of the parent compound and a table of endpoints. The table includes 'Acute Toxicity' (1/4, M: = 1.93E+03 mg/kg bdwt) and 'Repeated dose (HESS)' (Not categorized). Other endpoints like 'Bioaccumulation', 'Microbial metabolism simulator', and 'Observed Mammalian metabolism' are also visible.

**Step 1:** Generate in vivo metabolites upfront gap filling

Right click over the level with CAS# in the document tree and select in vivo Rat metabolism simulator. 9 metabolites are produced. The metabolites appeared next to the parent (see next slide).

# Handling of in vivo rat liver metabolism

The screenshot shows the QSAR Toolbox interface. On the left, the 'Documents' panel shows a tree structure for 'in vivo rat metabolism simulator' with metabolites #1 through #9. Below it, the 'Databases' panel lists various toxicity databases, with 'ECHA CHEM' and 'Food\_TOX Hazard EFSA' checked. The main window displays a table with columns for 'Parent chemical...' and 'metabolite #1' through '#9'. A 'Filter endpoint tree...' is visible on the left side of the table. Three callout boxes are present: '1' points to the 'Profile' section in the filter tree; '2' points to a row in the table where 'NOAEL' is highlighted in yellow; '3' points to a row in the table where 'Methyldopa' is highlighted in red.

**Step 2: Profile the package: parent and metabolites according to Repeated dose (HESS) profiler only** (uncheck the metabolic simulator)

Alerts are identified in four out of nine generated metabolites (1).

**Step 3: Gather data for package: parent and metabolites from the selected database** (gather only repeated dose toxicity data)  
Experimental data for the defined target endpoint is found for two of the metabolites (2).

The metabolite having an alert and available experimental data will be used for searching of analogues (3) (see next slide).

# 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.
- In our case we will use *Food TOX Hazard EFSA* database only in order to accelerate the work (before going to the Category definition module uncheck ECHA CHEM database). *ECHA CHEM* is not cached in advance and its metabolising will take some time.
- Searching for analogues will be based on a common metabolite (formic acid) generated as a result of *in vivo* Rat metabolism (see next slide)



# Category Definition

## Searching for analogues accounting for in vivo rat liver metabolism

The screenshot shows the QSAR Toolbox interface. The 'Category definition' module is active. A 'Select metabolism' dialog is open, showing a list of simulation options. The 'in vivo Rat metabolism simulator' is selected. A 'Grouping options' dialog is also open, showing a table of metabolites and their associated queries. Metabolite 9 is highlighted, and the 'exact' query is selected. A text box explains that the 'Exact' option is used for searching analogues with common metabolites. The 'OK' button is highlighted in the bottom right of the 'Grouping options' dialog.

Chemical	Query	Criteria
	none	No criteria.
	none	No criteria.
	exact	Matches exact structure.
	none	No criteria.

1. Go to **Category definition** module; 2. Click on the level with CAS:97530; 3. Click **Define with metabolism**; 4. Select **in vivo Rat metabolism simulator**; 5. Click **OK**; 6. Target and all metabolites produced by the selected simulator appear. Find the formic acid structure (Metabolite #9) and specify "**Exact**" query; 7. Execute the search by click **OK** (The selected databases are not cached. Therefore, first running of this example will take a few minutes).

# Category Definition

## Searching for analogues accounting for in vivo rat liver metabolism

The screenshot displays the QSAR Toolbox software interface. The main window is titled 'Category definition' and shows a search for '1 [target]'. A 'Read data?' dialog box is open, allowing the user to select endpoints. The 'Repeated Dose Toxicity' checkbox is checked. An information window indicates that 571 points were added across 156 chemicals. Below, a table shows search results for 'NOAEL' with 92/110 chemicals found.

Endpoint	Chemicals	Points	Molecular Weight (M)
NOAEC	2/2		
NOAEL	92/110	M: =300 mg/kg b...	M: =90 mg/kg M: =117 mg/kg... M: =58 mg/kg
NOEC	9/13		
NOEL	24/25	M: =250 mg/kg b...	M: =41 mg/kg b...
Sheep	4/4		
Turkey	2/2		
Sensitisation	AW SWAOP		

1. Click **Choose...** and select Repeated Dose Toxicity data to be collected only; 2. An information window appears informing about the number of experimental data collected and the number of chemicals in the category, click **OK**; 3. 92 chemicals with 110 experimental data has been found related to the target endpoint.

# 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 displays the QSAR Toolbox interface. The top navigation bar includes 'Data Gap Filling' (1). The left sidebar shows a document tree with 'Read across' (3) highlighted. The main area features a 'Filter endpoint tree' table:

Structure	1 [target]	2	3	4	5	6	7	8
Goat	1/1							
Goose	1/1							
Horse	1/1							
Japanese quail	15/20							
Mallard duck	83/162							
Mouse	3/3							
not reported	5/6							
Pig	2/2							
Quail	3/5							
Rabbit	0/10							
Rat								
NOAEC								
NOAEL	92/110	M: =300 mg/kg b...						
NOEC	9/1							
NOEL	24/25	M: =250 mg/kg b...						M: =41 mg/kg b...
Sheep	4/4							
Turkey	2/2							
Sensitisation		AW SW AOP						
ToxCast								
Toxicity to Reproduction								
Toxicokinetics, Metabolism and Distributi...								

The 'Possible data inconsistency' dialog box shows the following options:

- Native scale/unit:**
  - mg/kg (5 data; 4 chemicals)
  - mg/kg bdwt (2 data; 2 chemicals)
  - mg/kg bdwt/d (103 data; 86 chemicals)
- Gap filling scale/unit:**
  - log(1/mol/kg bdwt/d)
  - log(1/mol/kg)
  - mg/kg
  - mg/kg bdwt
  - mg/kg bdwt/d

The dialog also displays 'Data 103/110; Chemicals 86/92' and 'M: =58 mg/kg'.

1. Go to **Data Gap Filling** module; 2. Click the cell corresponding to the target chemical and defined endpoint.; 3. Apply **Read across**; 4. A pop-up window informing about possible data inconsistency appears click **OK**.

# Data Gap Filling

## Apply worst-case scenario

The screenshot displays the QSAR Toolbox interface during the 'Data Gap Filling' step. The 'Calculation options' panel on the right has 'Data usage' highlighted with a red box and labeled '1'. A 'Choose one' dialog box is open in the center, with the 'Minimal' radio button selected and labeled '2'. The 'OK' button in the dialog is labeled '3'. The background shows a scatter plot of NOAEL vs log Kow and a table of chemical structures with their respective NOAEL values.

Apply the worst case scenario: 1) Go to **Calculation options>Data usage**; 2) Click **Minimal** radio button; 3. Confirm with **OK**.

# Data Gap Filling Subcategorize

The screenshot displays the QSAR Toolbox interface with three subcategory selection windows (Sub.1, Sub.2, Sub.3) and a scatter plot. The subcategory windows show various chemical descriptors being selected. The scatter plot shows a read-across prediction for NOAEL based on 5 values, with observed values from 67 to 300 mg/kg bw/d and a predicted value of 56.3 mg/kg bw/d. A 'Select / filter data' menu is visible in the bottom right corner.

**Sub.1 Selections:**

- Organic functional groups, Norbert Haider (checkmol)
- Toxicological: Repeated dose (HESS)

**Sub.2 Selections:**

- Organic functional groups, Norbert Haider (checkmol)
- US-EPA New Chemical Categories

**Sub.3 Selections:**

- US-EPA New Chemical Categories
- General Mechanistic: Biodegradation ultimate (Biowin 3)

**Scatter Plot:**

Read-across prediction for NOAEL based on 5 values  
 Observed: from 67 to 300 mg/kg bw/d; Predicted: 56.3 mg/kg bw/d

**Select / filter data menu:**

- Select / filter data
- Subcategorize
- Mark chemicals by WS
- Mark chemicals by descriptor value
- Filter points by test conditions
- Mark focused chemical
- Mark focused points
- Remove marked data
- Clear existing marks

Go to **Select / filter data** > **Subcategorize** and apply the following subcategorizations: 1) Repeated dose (HESS); 2) Organic functional groups, Norbert Haider (checkmol); 3) US-EPA New Chemical Categories. Eliminate dissimilar chemicals after each of the applied subcategorizations using the "Remove selected" button

# Data Gap Filling Approach options

The screenshot displays the 'Data Gap Filling' workflow in the OECD QSAR Toolbox. A dialog box titled 'Choose prediction approach options' is open, showing radio button options: Median, Lower median, Higher median, Minimal, Maximal, **Arithmetic mean (average)**, and Geometric mean. The 'Neighbours count' is set to 7. A scatter plot below shows 'Observed' vs 'Predicted' values, with two points circled in red. A sidebar on the right shows 'Calculation options' with 'Prediction approach options' highlighted. A bottom banner provides step-by-step instructions.

**1. Go to *Calculation options* > *Prediction approach options*; 2. Define the *Neighbours count* to be 7 instead of 5; 3. Confirm by OK.**

The default Neighbour count for read across approach are set to 5. Therefore, two of the analogues do not take part in the prediction.

# Data Gap Filling

## Data variation

The screenshot displays the OECD QSAR Toolbox interface. The top menu bar includes 'Input', 'Profiling', 'Data', 'Category definition', 'Data Gap Filling', and 'Report'. The toolbar contains icons for 'Name', 'Structure', 'Composition', 'Select', 'ChemIDs', 'Database', 'Inventory', 'List', 'Substructure (SMARTS)', 'Query', and 'Define'. The 'Filter endpoint tree...' on the left shows a tree structure with 'Rat' selected. The 'Chemical List' table shows columns for 'Name', 'Structure', 'Composition', 'Select', 'ChemIDs', 'Database', 'Inventory', 'List', 'Substructure (SMARTS)', 'Query', and 'Define'. The table contains data for 'NOEL' and 'Sensitisation'. The 'NOEL' row shows '8/9' and 'M: =300 mg/kg...' for the first column, and 'M: =67 mg/kg b...' for the remaining columns. The 'Sensitisation' row shows '1/1' and 'M: =250 mg/kg...' for the first column. The 'Read-across prediction for NOEL' plot shows 'Observed: from 67 to 300 mg/kg bdwt/d; Predicted: 64.8 mg/kg bdwt/d'. The plot has 'log Kow' on the x-axis and 'NOAEL [log(1/mol/kg bdwt/d)]' on the y-axis. Two points are highlighted with red boxes: one at 3.31 log (1/mol/kg bdwt/d) and another at 3.47 log (1/mol/kg bdwt/d). A text box states: 'NOAEL is in the range from 3.31 to 3.47 log (1/mol/kg bdwt/d) for the 7 analogues'. The 'Calculation options' panel on the right includes 'Data usage', 'Prediction approach options', 'Use target data for prediction', 'Do not use target data for prediction', 'Set level of significance', 'Visual options', and 'Information'. A green checkmark and 'Accept prediction' button are at the bottom right.

- Target and analogues are grouped as a result of *in vivo* rat metabolism;
- They all generate common metabolite (formic acid), which may cause the toxicity effect;
- No significant variation of NOAEL is observed- over two magnitude
- In this respect, Scenario 5 should be applied

Read-across prediction for NOEL, based on 7 values  
Observed: from 67 to 300 mg/kg bdwt/d; Predicted: 64.8 mg/kg bdwt/d

NOAEL [log(1/mol/kg bdwt/d)]

log Kow

3.31 log (1/mol/kg bdwt/d)

3.47 log (1/mol/kg bdwt/d)

NOAEL is in the range from 3.31 to 3.47 log (1/mol/kg bdwt/d) for the 7 analogues

Accept prediction



# Data Gap Filling

## Category consistency check

The screenshot displays the QSAR Toolbox interface. The 'Category definition' module is active, and the 'Category consistency wizard' is open. The wizard's 'Wizard pages' list includes Physicochemical similarity, Structural similarity, Mechanistic similarity, (Eco)tox experimental data, and Options. The '2D/3D parameters' section is expanded, showing 'Parameters' (Boiling point, log Kow, Molecular Weight, Vapor Pressure, Water Solubility) and 'Physico-chemical data' (Boiling point, Partition Coefficient, Vapour pressure, Water solubility). The 'OK' button is highlighted with a red box and a '3'. The 'Accept prediction' button is highlighted with a red box and a '4'. The background shows a table of chemical structures and their predicted values for log Kow and NOEL.

After subcategorization process go back to the **Category definition** module (1) and apply **Category elements\*** (2). No different selection than the default is needed – click **OK** (3). Once the category elements are **applied** **accept** the prediction (4).

\*For more information on category elements see *Tutorial\_1\_TB 4.2. Category consistency*

## Recap

- In the *Category definition* module you found 246 chemicals having common metabolite (formic acid) as a result of in vivo rat metabolism.
- 92 out of all 246 chemicals have data for the defined endpoint.
- In *Data gap filling* module you applied a read-across approach. As a result of subcategorization the number of analogues was reduced to 7.
- Prediction approach options were changed in order the data for all seven analogues to be used for the prediction.
- No significant variation of NOAEL data was observed for the closest analogues.
- 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

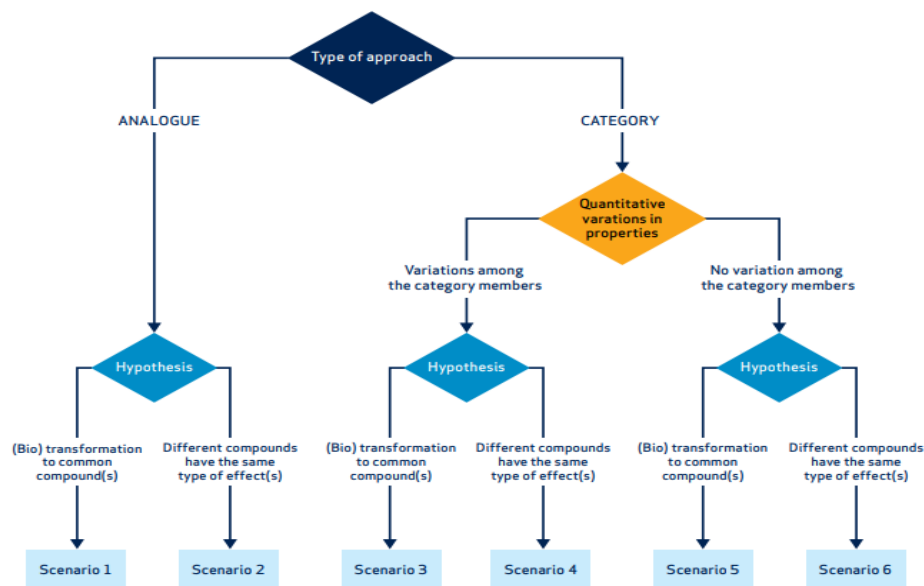
- Report module allows generating a report for any of the predictions performed within the Toolbox.
- The report module contains predefined report template which users can customize.
- Additionally specific RAAF scenario could be chosen. Selection of one of the scenarios will append automatically the 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](https://echa.europa.eu/documents/10162/13628/raaf_en.pdf)

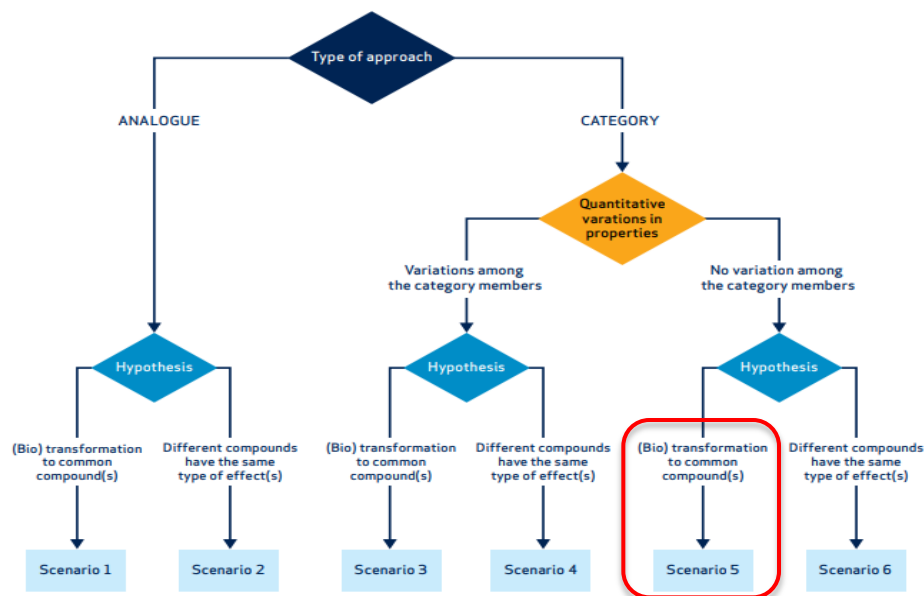
# Report

## Selection of RAAF scenario

For this example the following criteria are met :

- the type of approach applied - **category approach is used** (threshold of > 3 analogues is proposed by LMC for the category approach);
- the read-across hypothesis - **different compounds (bio)transformed to the common compound**;
- There is **no significant variation** in the property under investigation (NOAEL) among the category members

**Based on that RAAF scenario 5 was identified as the most appropriate for the current example.**



# Report

## Generation report according to RAAF-Scenario 5

The screenshot displays the QSAR Toolbox software interface. The top toolbar has the 'Report' icon highlighted with a callout '1'. The left sidebar shows the 'Prediction' icon highlighted with a callout '3'. The central area shows a table with a highlighted cell containing 'M: =300 mg/kg b...' with a callout '2'. The 'Customize report content and appearance' dialog box is open, showing the 'Add RAAF scenario' checkbox checked with a callout '4', and a dropdown menu with 'Scenario 5' selected with a callout '5'.

Structure	1 [target]	2
Common quail	2/2	
Dog	2/2	
Duck	1/1	
Goat	1/1	
Goose	1/1	
Horse	1/1	
Japanese quail	15/20	
Mallard duck	83/162	
Mouse	3/3	
not reported	5/6	
Pig	2/2	
Quail	5	
Rabbit	0	
Rat	0	
NOAEC		
NOAEL	92/111	M: =300 mg/kg b...
NOEC	9/13	
NOEL	24/25	M: =250 mg/kg b...
Sheep	4/4	
Turkey	2/2	
Sensitisation		AW SW AOP
ToxCast		
Toxicity to Reproduction		

1. Go to **Report** section; 2. Select a cell with prediction; 3. Click **Prediction**; 4. Check the box at the top to add RAAF scenario; 5. Select **Scenario 5** from the drop-down menu.

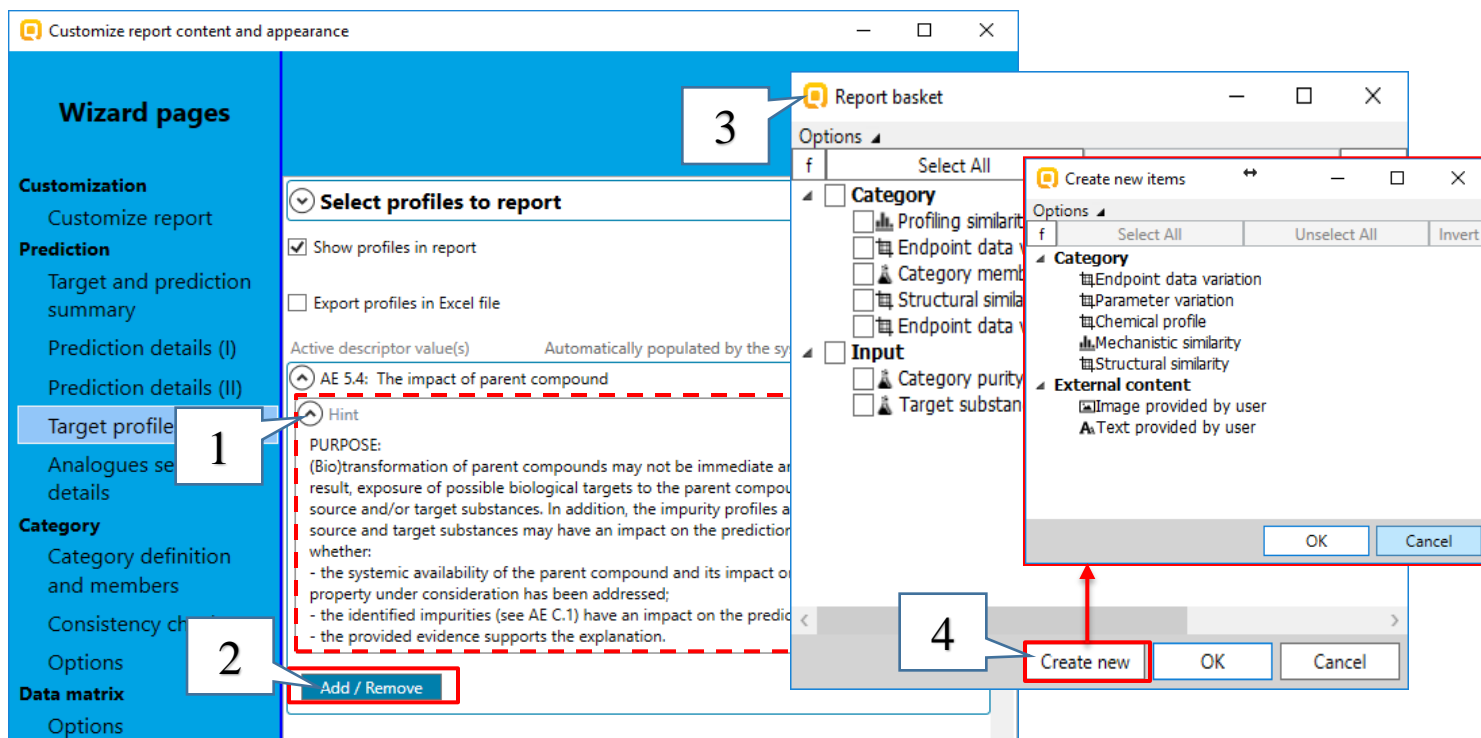
# Report

## Generation report according to RAAF-Scenario 5

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 5



Hint for each of the assessment elements is available (1). Information can be included by the **Add/Remove** button (2) located below the corresponding AE. The *Add/Remove* button invokes 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 5.4. The impact of parent compound**



# Report

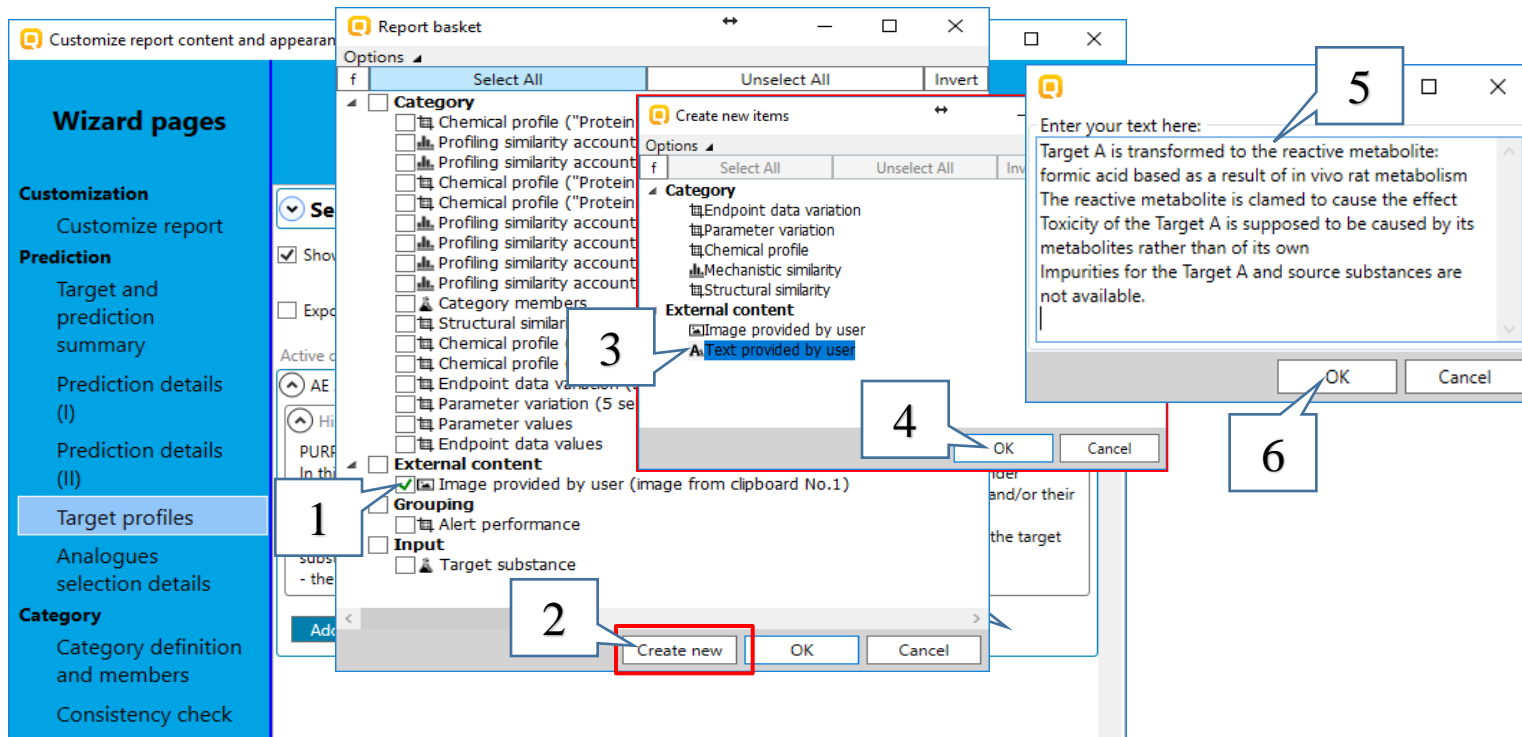
## Assessment elements of Scenario 5

Click on the **Add/Remove** button (1) and then **Create new** (2). Select to create 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 B, C, D, E, F, G** and **H** was prepared in advance.

# Report

## Assessment elements of Scenario 5



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:

- *Target A is transformed to the reactive metabolite: formic acid based as a result of in vivo rat metabolism*
- *The reactive metabolite is claimed to cause the effect*
- *Toxicity of the Target A is supposed to be caused by its metabolites rather than of its own*
- *Impurities for the Target A and source substances are not available.*

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

# Report Assessment elements of Scenario 5

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 details
- Category
  - Category of and membership
  - 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 5.4: The impact of parent compound

Hint

Add / Remove

Image provided by user (image from clipboard No.2) Edit Preview

Text provided by user (Target A and the sources C, D and E a) Edit Preview

Both newly created items appear under the **AE 5.4**. (1). Each of the items can be **edited** (2) or just **previewed** (3) in a .pdf format. Example on how the AE 5.4. and related description will look in the generated report is shown in right (4).

Prediction of NOAEL for Eugenol 4 / 6

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

**Profiles used for grouping/subcategorization**

Using of "in vivo Rat metabolism simulator" Product requirement 1. Exactly this structure: OC=O (primary grouping)	metabolite #1; Is not: OC=O; metabolite #2; Is not: OC=O; metabolite #3; Is not: OC=O; metabolite #4; Is not: OC=O; metabolite #5; Is not: OC=O; metabolite #6; Is not: OC=O; metabolite #7; Is not: OC=O; metabolite #8; Is not: OC=O; metabolite #9; Is exactly: OC=O
Repeated dose (HESS) (subcategorization)	Not categorized
Organic functional groups, Norbert Haider (checkmol) (subcategorization)	Alkene; Alkylarylether; Aromatic compound; Ether; Hydroxy compound; Phenol
US-EPA New Chemical Categories (subcategorization)	Phenols (Acute toxicity)

log Kow (calculated): 2.73

**AE 5.4: The Impact of parent compound**

**1. Image provided by user (image from clipboard No.3)**

Target A | Source B | Source C | Source D | Source E | Source F | Source G | Source H

Target A is transformed to the reactive metabolite: formic acid based as a result of in vivo rat metabolism  
 The reactive metabolite is claimed to cause the effect  
 Toxicity of the Target A is supposed to be caused by its metabolites rather than of its own  
 Impurities for the Target A and source substances are not available.

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

# Report Assessment elements of Scenario 5

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
  - Options
- Data matrix
  - Options

**Profiles/Metabolisms**

**Category members**

AE C.1: Substance characterization

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 5.1: Formation of common (identical) compound(s)

AE 5.2: The biological targets for the common compounds

AE 5.3: Exposure of biological targets to the common compounds

AE 5.5: Formation and impact of non-common compounds

AE C.1: Substance characterization

Hint

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





Add / Remove

2

1.5. Category members  
AE C.1: Substance characterization

manually editable field

Category members

#	CAS	Name	SMILES	Structure
1	97-53-0	Eugenol	CCc1cc(CC=C)ccc1O	
2	6766-82-1	2,6-Dimethoxy-4-propylphenol	CCCCc1c(OC)c(O)c(OC)c1	
3	2785-87-7	Dihydroeugenol	CCCCc1cc(O)c(O)c1	
4	14059-92-8	4-Ethyl-2,6-dimethoxyphenol	CCc1cc(OC)c(O)c(OC)c1	

QSAR Toolbox 4.2  
Database version: 4.2

QSAR TOOLBOX

TPRF v4.2

1





Five AE (AE C.1, 5.1, 5.2, 5.3 and 5.5) related to Scenario 5 are included in the *Category definition and members* section .

- **AE C.1 Substance characterization** is separated into two parts. The first part is automatically filled (1) by the system using the available items in the *Report basket*.

Example on how the AE C.1. will look in the generated report is shown in right (2).

Chemicals category

3 / 40

5	2785-89-9	4-ethylguaiacol	CCCc1cc(O)c(O)c1	
6	6638-05-7	2,6-dimethoxy-p-cresol	CCc1cc(C)cc(OC)c1O	
7	93-51-6	Cresol	CCc1cc(C)ccc1O	
8	6627-88-9	4-Allyl-2,6-dimethoxyphenol	CCc1cc(CC=C)cc(OC)c1O	

# Report

## Assessment elements of Scenario 5

- **AE C.1 Substance characterization:** Click **Add/Remove** button in the second part of AE C.1. Check the box next to *Category purity/impurity* item (2). Right click over the item and select **preview** to see the content (3). Finally confirm by **OK** (4).

# Report Assessment elements of Scenario 5

**AE 5.1: Formation of common (identical) compound(s)** - Click on the **Add/Remove** button (1) and create new item with textual content (see slide 45).

In the text field you paste the following example text:

- *Formic acid is produced from the target substance A and the source substances B-H by in vivo rat metabolism simulator*
- *Alert for repeated dose toxicity and experimental data for the property under consideration are found for the common metabolite.*

Once the text item is created (2), check the box next to the *Common product* tem (3). Right click over the item and select **preview** to see the content (4). Finally confirm by **OK** (5).

# Report Assessment elements of Scenario 5

The screenshot shows a software 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 (AE) with their respective "Hint" and "PURPOSE" sections. Red boxes highlight each AE section, and red arrows point from these boxes to corresponding example text blocks on the right side of the slide.

## Example text for AE 5.2: The biological targets for the common compounds

- The target and source substances form a common metabolite: formic acid.
- No alerts are identified in the structures of the Target A and Source substances B-H.
- The common compound is supposed that may cause the toxic effect.

## Example text for AE 5.3: Exposure of biological targets to the common compounds

- Target chemical A and source substances from B to H are metabolized to the common reactive product: formic acid;
- It well known from the literature [1-3] that some carboxylic acids induce adverse effects in the liver. It is expected that the exposure of the biological targets to the common product vary in a predictable manner.

### References:

1. Casarett & Doull's Toxicology, Curtis D, Klaassen-7<sup>th</sup> ed, McGraw-Hill companies, USA(2007)
2. New edition Toxicology, edit by Japanese society of Toxicology, Japan(2009)
3. Toxicology in Medicine, Tetsuo Sato-4<sup>th</sup> ed, Nankodo, Japan (2010)

## Example text for AE 5.5: Formation and impact of non-common compounds

- The target substance A and the seven source substances (analogues) are metabolized to the common- formic acid and non-common compounds (including possible intermediates)
- Hepatotoxicity might be caused due to the common compound
- Also the positive effect of formic acid is supported by experimental NOAEL data.
- Another alerts related to Hepatotoxicity and Renal toxicity are identified in some of the produced non-common compounds.
- The lowest experimental NOAEL value was found for the common metabolite.
- The common compound is supposed to be responsible for the repeated dose toxicity effect.

# Report

## Assessment elements of Scenario 5

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

AE C.3: Link of structural similarity and differences with the proposed regular pattern

Hint

PURPOSE:  
It has to be assessed whether:

- the documentation provides an explanation why the category members should behave in a predictable manner (e.g. based on no absorption due to molecular-weight considerations, or lacking reactivity towards biological material, regular pattern in increasing strength of effect due to kinetic differences);
- it is likely that all category members follow the proposed explanation and where the boundaries of the category are in this respect; and
- the provided evidence supports the explanation.

Add / Remove

AE C.6: Bias that influences the prediction

Hint

PURPOSE:  
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).

Add / Remove

Back Next Cancel Create report

Example text for **AE C.3: Link of structural similarity and differences with the proposed regular pattern**

- *The category is structurally defined as target (A) and seven source substances (B, C, D, E, F, G, H) all form a common product – formic acid*
- *They all consist of common reactivity pattern responsible for the formation of reactive metabolites*

Example text for **C.6: Bias that influences the prediction**

- *Source substances for the target chemical A have been searched based on formation of a specific metabolite as a result of in vivo rat metabolism;*
- *All found analogues that have repeated dose toxicity alert as a parent have been removed in order to be consistent with the target.*
- *On the next level all analogues that differ from the Target A according to OFG, Norbert Haider and US-EPA New Chemical Categories profiling schemes have been removed.*
- *Seven source substances with no significant variation in the property under consideration were used for the prediction.*

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



# Report

## Assessment elements of Scenario 5

Customize report content and appearance

**Wizard pages**

- Customization
- Prediction
- Category
- Consistency check
- Options
- Data matrix

**Structural similarity**

Justification for selected structure similarity profilers

Add / Remove

Structural similarity Edit Preview

Chemical profile ("Organic functional groups, Norbert Haider (checkm) Edit Preview

Chemical profile ("Organic functional groups") Edit Preview

Chemical profile ("Structure similarity") Edit Preview

**Comments on structural similarity**

AE C.2: Structural similarity and structural differences within the category

Hint

PURPOSE:  
The aim of this AE is to verify that all category members indeed meet the criteria for structural similarities and allowed structural differences used for the category description. It has to be assessed whether:









- the structural similarities identified apply to all category members; and
- there are structural differences which are allowed within the category.

Add / Remove

**Calculated structure similarity**

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	Chemical 5	Chemical 6	Chemical 7	Chemical 8
Chemical 1	100%	46.2 %	75 %	48 %	78.3 %	41.7 %	72.7 %	69.2 %
Chemical 2	46.2 %	100%	69.2 %	88.9 %	56 %	76.9 %	41.7 %	78.6 %
Chemical 3	75 %	69.2 %	100%	56 %	87 %	41.7 %	72.7 %	46.2 %
Chemical 4	48 %	88.9 %	56 %	100%	66.7 %	80 %	43.5 %	81.5 %
Chemical 5	78.3 %	56 %	87 %	66.7 %	100%	43.5 %	76.2 %	48 %
Chemical 6	41.7 %	76.9 %	41.7 %	80 %	43.5 %	100%	63.6 %	76.9 %
Chemical 7	72.7 %	41.7 %	72.7 %	43.5 %	76.2 %	63.6 %	100%	41.7 %
Chemical 8	69.2 %	78.6 %	46.2 %	81.5 %	48 %	76.9 %	41.7 %	100%

**Chemical profile ("Organic functional groups, Norbert Haider (checkmol)")**

1	2	3
		
Hydroxy compound Phenol Ether Alkylarylether Alkene Aromatic compound	Hydroxy compound Phenol Ether Alkylarylether Aromatic compound	Hydroxy compound Phenol Ether Alkylarylether Aromatic compound
4	5	6
		
Hydroxy compound Phenol Ether Alkylarylether Aromatic compound	Hydroxy compound Phenol Ether Alkylarylether Aromatic compound	Hydroxy compound Phenol Ether Alkylarylether Aromatic compound
7	8	
		
Hydroxy compound Phenol Ether Alkylarylether Aromatic compound	Hydroxy compound Phenol Ether Alkylarylether Aromatic compound	

**AE C.2. Link of structural similarity and structural differences within the category is related to the structural similarity of the final category.**

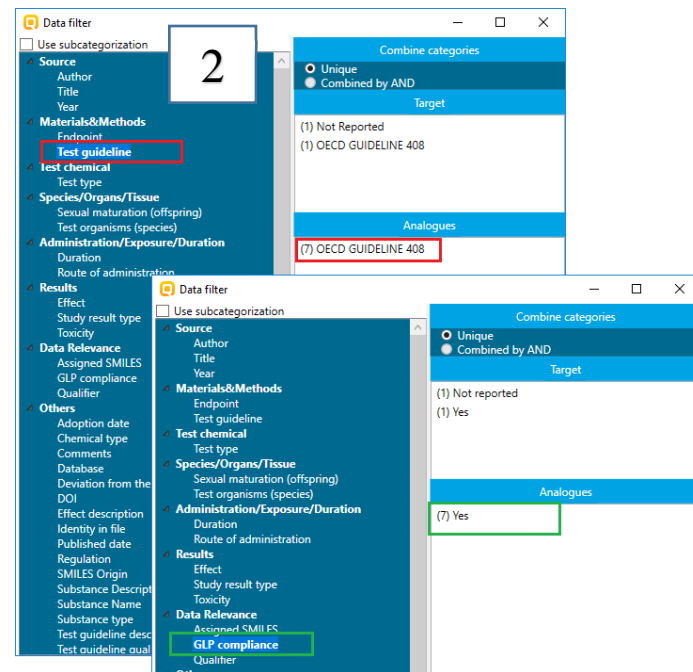
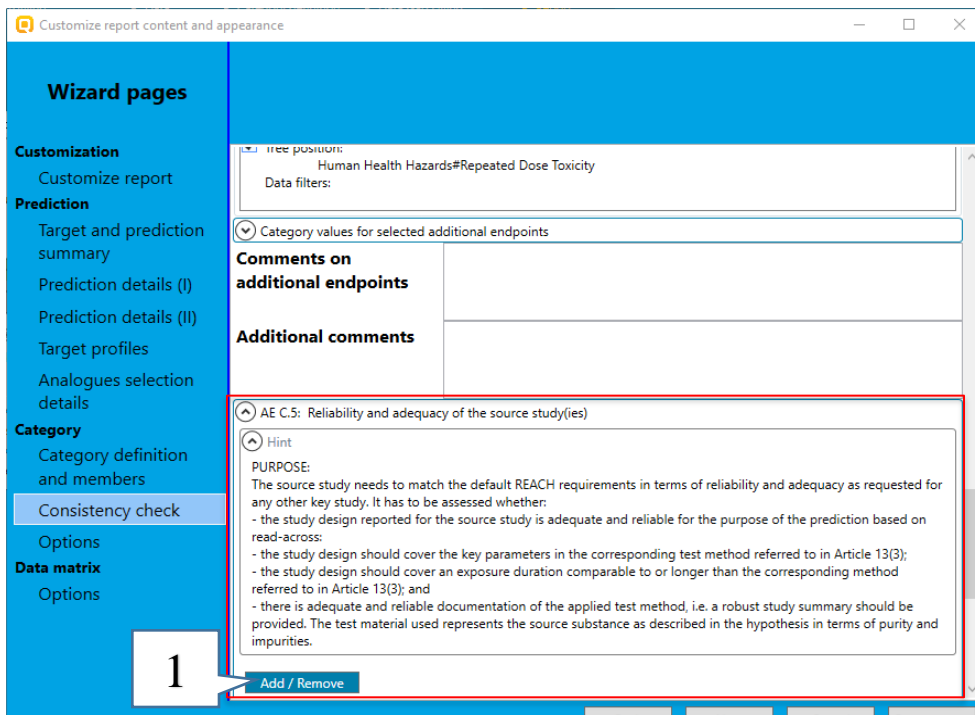
All items in the report basket related to the structural consistency of the category (1) are added automatically.

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

- *Structural similarity between Target substance A and the seven source substances B - H is in the range of [42-89%] according to the default settings of the Structure similarity profiler*
- *"Hydroxy compound", "Phenol", "Ether", "Alkylarylether" and "Aromatic compound" categories of the OFG, Norber Haider profiler are identified in all category members.*

# Report

## Assessment elements of Scenario 5

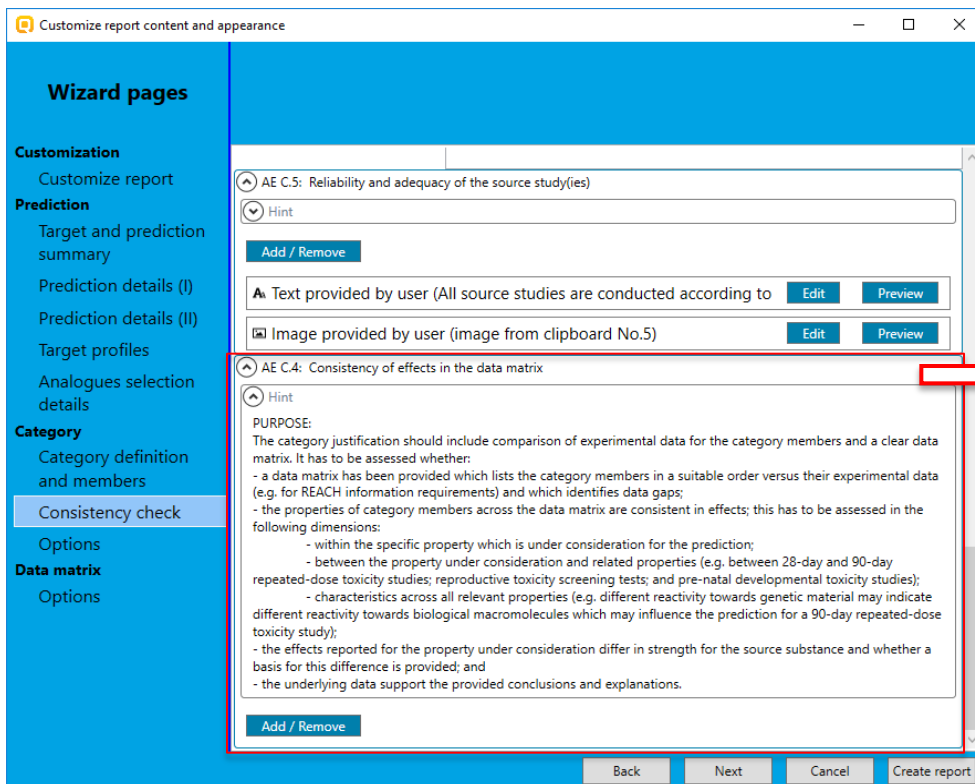


**AE C.5: Reliability and adequacy of the source study(ies)**  
 The following example text can be added for AE C.5. (2):

- All source studies are conducted according to OECD Test Guideline 408: Repeated Dose 90-day Oral Toxicity Study in Rodents.
- All source studies are in compliance with the principles of Good Laboratory Practice.

Additionally snapshots of the filter by test conditions window (2) could be added to confirm the consistency regarding the guideline and GLP compliance.

# Report Assessment elements of Scenario 5



## AE C.4: Consistency of the effects in the data matrix

The following example text can be added for AE C.4. (2) by analyzing the structural similarity items:

- *Physico-chemical properties, identified alerts and experimental data along with the characteristics of the studies (species, duration, test type, references, etc.) are provided in the generated Data matrix file.*

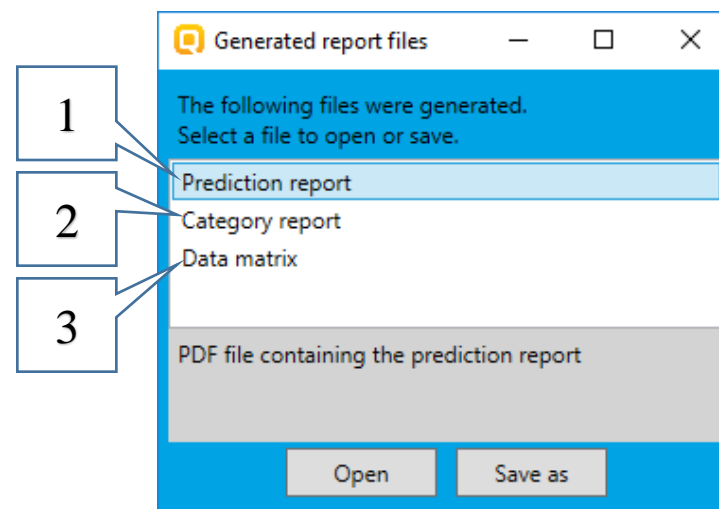
# Report Generation report

After the click on the 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

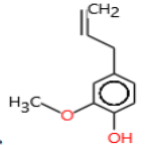
Prediction of NOAEL for Eugenol 1 / 6

## Prediction report

**QSAR Toolbox prediction for single chemical**  
(In accordance with RAAF scenario 5)

Date: 30 Mar 2018  
Author(s):  
Contact details:

Structural Information	Target Information	Chemical names
<b>SMILES:</b> <chem>COc1cc(CC=C)ccc1O</chem>	<b>CAS#:</b> 97-53-0 <b>Other:</b> EC Number:4074682	[eugenol]eugenol (4-allyl-2-methoxypheno[1]4-allyl-2-methoxy-phenol[4-allyl-2-methoxy-phenol],2-methoxy-4-(2-propenyl)-[eugenol 1-ALLYL-3-METHOXY-4-HYDROXYBENZENE



Chemicals category 1 / 40

## Category report

**QSAR Toolbox report for category**  
(In accordance with RAAF scenario 5)

**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	230 ÷ 298	°C
log Kow	1.71 ÷ 2.87	<no units>
Molecular Weight	138 ÷ 196	Da
Vapor Pressure (Antoine method)	0.000166 ÷ 0.0638	mm Hg
Water Solubility	228 ÷ 2.17E+03	mg/L

## Data matrix report

	Target chemical	Neighbour #1	Neighbour #2	Neighbour #3	Neighbour #4	Neighbour #5	Neighbour #6	Neighbour #7
1 Substance Identity								
2 Structure								
3 CAS number	97-53-0	6766-82-1	1785-87-7	14059-92-8	2785-89-9	6638-05-7	93-51-6	6627-88-9
4 Chemical name	Eugenol	2,6-Dimethoxy-4-Allylanisole	Dihydroeugenol	4-Ethyl-2,6-dimethoxyphenol	4-ethylguaiacol	2,6-dimethoxy-p-cresol	Cressol	4-Allyl-2,6-dimethoxyphenol
5 Other identifier								
6 SMILES	<chem>COc1cc(CC=C)ccc1O</chem>	<chem>COc1cc(OC)cc(OC)c1</chem>	<chem>COc1ccc(O)cc1</chem>	<chem>CCc1cc(OC)cc(OC)c1</chem>	<chem>CCc1cc(OC)cc(OC)c1</chem>	<chem>COc1cc(OC)cc(OC)c1</chem>	<chem>COc1cc(OC)cc(OC)c1</chem>	<chem>COc1cc(OC)cc(OC)c1</chem>
9 Parameters								
10 Vapor Pressure (Antoine)	0.00965	0.000186	0.00207	0.000559	0.0261	0.00194	0.0638	0.000183
11 log Kow	2.73	2.89	2.87	2.2	2.38	1.71	1.88	2.56
12 Molecular Weight	164	196	166	182	152	168	184	194
13 Boiling point	264	298	266	282	248	266	230	297
14 Water Solubility	754	230	228	709	694	2.17E+03	2.09E+03	307
15 Profiles								
17 Profiles used for US-EPA New Chemical Categories, with	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C	metabolite #1, to avoid (P)H-C
18 Repeated dose (HESI)	Not categorized	Not categorized	Not categorized	Not categorized	Not categorized	Not categorized	Not categorized	Not categorized
20 Organic functional groups, Norbert	Aliene,	Allylarylether,	Allylarylether,	Allylarylether,	Allylarylether,	Allylarylether,	Allylarylether,	Allylarylether,
21 Prefdefined								
22 US-EPA New Chemical Categories, with	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),	Phenols (Acute toxicity),
23 Organic functional groups	alkene, ether,	ether,	ether,	ether,	ether,	ether,	ether,	alkene, ether,
24 Structure similarity	[90%,100%]	[40%,50%]	[70%,80%]	[40%,50%]	[70%,80%]	[40%,50%]	[70%,80%]	[60%,70%]
26 Toxicological								
27 Repeated dose (HESI), with in vivo Rat	Not categorized,	Not categorized,	Not categorized,	Not categorized,	Not categorized,	Not categorized,	Not categorized,	Not categorized,
28 Measured and predicted data								
29 Data used for prediction								
31 environment	endpoint value unit species duration, test	value unit species duration, test	value unit species duration, test	value unit species duration, test	value unit species duration, test	value unit species duration, test	value unit species duration, test	value unit species duration, test
32 Repeated Dose Toxicity	NOAEL	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic	67 mg/kg bw/d 90-d Subchronic
33 Physical Chemical Properties/Boiling								

**5 selected: Physical Chemical Properties#Boiling point; Physical Chemical Properties#log Kow; Physical Chemical Properties#Molecular Weight; Physical Chemical Properties#Water solubility; Physical Chemical Properties#Vapor Pressure**  
*2D parameters data variation*

Variation	unit (family)	Number of chemicals
221 ÷ 253	°C(Temperature)	4
0.0226	mm Hg(Pressure)	1
0.04	Pa(Pressure)	1
1.15E+03 ÷ 2.46E+03	mg/L(Mass concentration)	2
1.83 ÷ 67.6		3

**point(s)** *manually editable field*  
Repeated Dose Toxicity: NOAEL, Rat *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 5.
- Note proficiency comes with practice.